# PSYCHOPHYSIOLOGICAL MECHANISMS IN SKIN DISEASES

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THE extent to which emotional stress is a factor in the ætiology of skin diseases has long been a popular source of speculation.

Skin conditions account for about 10% of disease encountered in general practice (Logan and Cushion 1958), and the response to treatment is very variable. Often where physical remedies prove ineffective, psychological factors are invoked; and conversely, when a psychological approach fails, resistant physical factors in the skin lesion are blamed. While the physician recognises that both factors play a part, this essential interaction is poorly understood. Insufficient understanding of the means whereby psychological stress can bring about specific physiological or pathological change in the skin has led to perplexity both in classification and treatment of these conditions. Consequently there is a need to formulate some heuristic concept for our guidance.

### Traditional Psychodermatological Concepts

The skin is a sensitive indicator of emotional disorder, and most authorities hold that certain groups of skin lesions are of psychogenic origin: Brocq and Jacquet coined the term neurodermatitis in 1891; Kriebich (1924) postulated that eczema resulting from pruritus vulvæ was caused by sexual frustration; mother fixation and sado-masochistic trends have also been blamed (Stokes 1930); and English (1949) cited inferiority feelings and the need for love as strong emotions likely to cause skin manifestations. These psychoanalytical views are based on the concept that repressed emotion must seek some outlet, and that certain skin diseases represent this exteriorisation of stress release.

Attention has been paid to patterns of personality: Rogerson (1934) allied eczema with personality disorders in childhood; Klaber and Wittkower (1939) suggested that patients with social anxiety were prone to rosacea; and MacKenna (1944) found that anxious, hysterical, narcissistic, and obsessional personality-types were common in dermatological practice.

Generally it has been held that some skin diseases represent an expression of psychobiological imbalance (Lynch et al. 1945). Becker and Obermeyer (1947) produced their classification of the neurodermatoses, which contained most diseases known to have psychological implication, and the work of Dunbar (1943) and Cormia (1947) did much to promote the understanding of psychosomatic dermatology. The concept held by most practitioners accords with that of Wittkower and Russell (1953)—namely, that certain skin diseases are induced by psychological factors, that psychological factors are contributory in some other skin diseases, and that in many other skin conditions psychological factors are of no significance.

### Some Recent Findings

Evidence has been presented, however, that mental stress may merely be a factor in the neurodermatoses rather than their cause. Macalpine (1958) questioned psychic trauma as the cause of alopecia areata in low-grade imbeciles; and Borrie (1959), who thought that few skin diseases are induced by psychological mechanisms, suggested that the part played by emotional factors was contributory in prolonging or aggravating such lesions.

Additional evidence that psychological factors are not of overriding importance in the ætiology of the neurodermatoses has recently come to light. First, neurodermatoses have been found in schizophrenic patients who exhibited a decreased affective response; because these patients were pathologically limited in their means of expressing or repressing emotion, it was difficult solely to implicate stress mechanisms in the causation of their skin lesions (Kidd and Meenan 1961a). A further study (Kidd and Meenan 1961b) of a mentally defective population in which impairment of psychophysiological mechanisms is clear, disclosed that these patients had neurodermatoses, though one would expect persons of such low intelligence to show little emotional repression and stress somatisation.

The importance of this recent evidence is that psychological factors, while known to be integrally tied up with certain groups of skin diseases, may nevertheless be slight or even absent in the same diseases. Because lesions traditionally attributed to stress may occur in situations of psychophysiological impairment, the concept that the neurodermatoses are entirely of psychogenic origin must be reviewed, and the mechanisms of psychosomatic effect examined.

### The Meaning of "Psychosomatic Effect"

It seems probable that the strengths of the components (*organic* and *psychological*) which make up a psychosomatic condition must vary, and it is reasonable to postulate that the clinical course of a psychosomatic disease is governed by variability in the relative dominance of the two components. This is shown if either organically oriented or psychologically oriented therapy proves efficaceous in the neurodermatoses. Apparent cure can follow without any overt psychological treatment; conversely, it is widely known that many psychological treatments can help or bring about complete naked-eye remission in some psychocutaneous diseases. If a psychosomatic effect can be reversed in response to widely differing forms of psychological therapy, these therapies must have an essential common factor.

Many psychoanalysts have postulated a relation between the skin and emotional conflict (Alexander 1950, Wittkower and Russell 1953, Klein 1954), yet it is doubtful

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whether all people showing these conflicts suffer from skin diseases as a consequence. Nevertheless in psychoanalytical practice it is often found that a skin lesion has remitted during treatment.

Since Bernheim (1836), workers using " suggestion " with or without hypnosis have reported remissions. The actual mechanisms underlying this process are ill understood, though it is presumed that the effect of suggestion on the patient activates the nervous system and sets in motion complex physiological adjustments.

Cure is sometimes seen as a placebo reaction, where suggestion, if not overt, is implied. The patient may not be promised a cure, but the subjective feeling that something is being done may bring this about.

Psychotropic drugs, too, may facilitate the remission of skin disorders by altering the patient's mental state. Cases 1 and 2 illustrate this action:

**Case 1**

A single man, aged 34, was admitted for psychiatric treatment of a schizo-affective psychosis. For 10 years he had had extensive psoriasis affecting mainly scalp and limbs. A course of imipramine was started for his depressive symptoms; 24 hours later he complained that his skin was " on fire ", and he appeared to be entering an acute phase of psoriasis. After 3 days there was considerable desquamation; within a week he announced that his skin condition was " better than it had been for years ", and at the end of 11 days his psoriasis was in a state of complete remission. His mental state had commensurably improved. The remission of his skin lesions was still complete 4 months later.

**Case 2**

A single male doctor, aged 46, was admitted for psychiatric treatment of alcoholism and depression. For over 20 years he had had extensive psoriasis affecting trunk and limbs. He was given a course of imipramine, and told that it would benefit his skin disease, which he refused to believe. 24 hours later he too complained of a sensation of burning; this lasted for 4 days during which he could not leave his bed. Desquamation followed in a week. After 3 weeks his psoriasis was much improved, though not in complete remission; it was still quiescent 4 months later.

The first patient expected the drug to act upon his skin, and this action was potentiated by the specific effect of the drug upon his nervous system; he felt different and therefore thought that something must be happening to his skin. In case 2 the drug apparently did not produce this expectancy effect, yet its action on the patient's brain was enough to make him feel that something was happening to his psoriasis despite his scepticism. As there is no reason to believe that imipramine has any selective antipsoriatic effect, these remissions were probably brought about indirectly by relief of psychological dysfunction.

The common factor in these therapeutic approaches is the force of suggestion. This may be specific (as in suggestive therapy and placebo reactions) or non-specific in altering the mental state by means of drugs, and in psychoanalysis.

Although specific suggestion is avoided in psychoanalytical treatment, the subjective feeling of altered emotional state resulting from the ventilation of psychological conflicts places non-specific suggestion in a dominant role.

Dollard and Millar (1950) defined a psychosomatic effect as " an innate physiological reaction to a state of ' high drive ', or some consequence of a learned response ". It is plausible to believe that the psychoanalytic approach deals with the intrinsic state of emotional high drive in an empirical way, while specific methods of suggestion appear to bring about physiological readjustment without direct reference to the state of high drive in the patient.

### Experiment in Psychophysiological Action

The action of psychosomatic effect bears much resemblance to the physiological changes observed in hypnotised subjects—by Weitzenhoffer (1953), Dunbar (1954), Bykow (1957), Schultz and Luthe (1958), and Bethune (1960a), to name but a few.

The simplest psychosomatic effect is probably seen in " ideomotor action " (Hull 1933, Eysenck 1957). Suggestions of movements are made to the subject, and these give rise to a subjective feeling of movement, soon followed by real movement. In the first place the subject perceives himself moving although his body is quite still, and this distortion of his body percept then results in real movement, obviously by initiating some action within the central nervous system. The movement once initiated is potentiated by a feed-back from the now moving muscles and joints. The suggestion of movement evokes emotional arousal as well as attention to the supposedly moving muscles, in that the subject feels he is being influenced. This may well provide the high drive of Dollard and Millar's definition.

More complex physiological events in areas under autonomic control can also be initiated by induced ideation. One of us (Bethune 1960a) has suggested that the terms " ideovascular " and " ideovisceral " are descriptive of these specific psychophysiological effects. It can be shown experimentally that stomach contractions will cease when a hungry subject under hypnosis " eats " an " hallucinated " meal. This is ideovisceral action. Ideovascular action can be demonstrated by suggesting to a hypnotised subject that a radiator is directed on his ear; the ear will become hot. This is a local vascular phenomenon induced by ideation.

We postulate that three components are relevant in these psychophysiological phenomena induced in the laboratory:

A state of emotional high drive, which is an inevitable accompaniment of the induction of the hallucinated stimulus. High drive initiates activity of the central nervous system.

The subjective feeling of the physiological response directs efferent nerve impulses to the organ or part which is now the seat of subjective sensation. This initiates ideovisceral or ideovascular action.

Ideovisceral or ideovascular action is sustained and reinforced by afferent feedback from the organ or parts involved.

Experimental evidence supports this theory: it has been shown that actions once evoked by appropriate hallucinations can later be caused to appear as responses to " emotional learning " (Bethune 1960b). Hallucinated subjects who were told that a heater was directed towards the left ear had a subjective feeling that the ear was hot, and there was also an objective increase in temperature. Using a form of " instrumental conditioning " this phenomenon was then induced in an hallucinated stress situation; and even though the patient was not under hypnosis the ear became hot in everyday stress conditions away from the laboratory. This ideovascular event conforms with Dollard and Millar's criteria for psychosomatic effect in that it appeared as " some consequence of a learned response ".

### Clinical Application of this Concept

We contend that if physiological dysfunction can be initiated by psychological stimuli applied in a laboratory, this also can and does happen in everyday human experience.

Adler (1914) and Wolff (1952) emphasised that organ selection in psychosomatic effects was often determined by basic " organ inferiority ", inherited or acquired. If an organ is weak, ideovisceral or ideovascular activity may become directed to that organ simply because the patient has " learned " to become conscious of subjective feelings there. In some cases the impact of continued emotional concern (high drive) about a disfigurement and its social disadvantages may " fix " the lesion by its morbid ideovisceral or ideovascular responses. This, we think, may account for failure in response to suggestive therapy. When this occurs, treatment should be based on the redirection of the high drive.

There is little doubt that psychological stimuli can bring about some anatomical change; evidence has been put forward in reports of successful cures of skin diseases (Mason 1952, 1955, Asher 1956, Sinclair-Gieben and Chalmers 1959, Ullman and Dudek 1960). Here the train of events has simply been in a curative rather than a morbid direction.

The following cases illustrate the relative importance of these psychological variables in skin conditions with an unquestionable organic substrate:

**Case 3**

A single woman, aged 29, had been affected since birth with ichthyosis involving her neck, shoulders, chest, buttocks, and limbs. Seasonal regression occurred during each late spring. The patient's father and one sister were similarly affected. Her attitude was of the typical " leper complex ". In an effort to cover her skin she had never worn dresses or skirts. She felt limited in normal social and vocational relationships, and was virtually imprisoned by her condition.

She was asked to read a case-report of the successful treatment of a similar condition (Mason 1952), and she was treated by hypnosis to induce subjective feelings of changes in the skin. In the 3rd week of treatment exfoliation began. 2 weeks later the condition had regressed to the extent that for the first time in her life she felt confident to wear woman's clothing. 7 weeks from the start of hypnotherapy the patient had reached a state of complete naked-eye remission.

4 years later she was still apparently cured. Since the remission she has been able to follow an unrestricted and healthy vocational and social life.

**Case 4**

A single electrician, aged 23, had moderately severe congenital ichthyosis affecting his chest and limbs, with seasonal regression during the warmer months. His maternal grandfather and mother also had this condition. He was shy and introspective, and sensitive about the appearance of his skin.

Treatment followed the same lines as in case 3. The early result was not so striking, and after 6 months he had an incomplete relapse. But this was shortly followed by a complete remission, which has remained. This remission was associated with a determined redirection of drive by the patient himself: he took steps to realise a long-held ambition, started at the university, and has become sociable and content.

**Case 5**

A married railway porter, aged 40, had had dermatitis/eczema, involving the neck and flexural areas of the limbs, for about 12 years, with varying periods of remission. Topical applications tended to alleviate, but never to resolve, the condition.

An attempt to induce a perceptual distortion that there was no itching was easily accomplished, but it did not persist. The patient remained discontented, and treatment appeared to be only palliative. His wife reported that he was fully preoccupied with his skin: when in a state of partial palliation he was concerned with how long this was likely to last. The home situation was tense, and the entire family liable to episodes of unhappiness.

During the interview the wife complained that her limbs were always cold. She was, in fact, having daily episodes of Raynaud-like symptoms affecting all four limbs. She consented to a test trial of hypnosis, and the condition subsided when she was hallucinated and thought she was in a warm bath. It was suggested to her that important factors leading up to the present situation would become clear to her. Immediately she became highly emotional, and was aroused from the hypnotic state. It transpired that as a teenager she had been a victim of rape, and she had a consequent horror of sexual relations. She had always avoided intercourse when possible during her married life; but she was very much in love with her husband and plied him with gifts and affection as a substitute for normal marital relations.

The husband was again interviewed, and this matter was raised. He agreed that their sexual relations were unsatisfactory, that he felt he was merely being mothered, and that he had long since become impatient with the whole family situation.

The wife rapidly responded to psychotherapy, and her episodes of limb vasospasm ceased with the resumption of normal marital relations. The husband then found that when perceptual distortion was induced it lasted; and with the help of topical applications his eczema entirely resolved. 8 months later, both husband and wife were essentially free from eczema and vasospasm. The husband is aware of his skin " weakness ", and he can deal with the start of any itching by autosuggestion. Both were very happy, and all home tensions had been resolved.

**Case 6**

A housewife of 33 had had psoriasis affecting the scalp, and also a small area on the sternum and perineum, for 12 years. She was predominantly concerned with excoriation in the vulval area which caused dyspareunia. Because she was grossly overweight, she was the victim of many unkind remarks, and she had become shy and had withdrawn from most social contacts.

A perceptual distortion of " no discomfort " was easily induced, and it was pointed out that the gross compression of her skin creases caused by her obesity had rendered useless topical applications to her perineal lesions. Reference to her obesity produced a tearful outburst, and she professed that unhappiness due to either dyspareunia or obesity made her want to eat.

She was supported through a period of strict dietary regime, during which she lost 4 st. (56 lb.) in weight. She soon was able to resume normal sexual relations without discomfort, and when she had lost about 2 st. her perineal lesions healed completely. 2 months later the scalp also cleared. The chest still shows mild postpsoriatic changes which do not bother her. She has become an attractive girl, and she now copes with a responsible job as well as her family commitments.

All these patients still have this underlying skin anomaly or organ inferiority which predisposes them to their own particular malady. We do not claim to have cured any of them. Their psychological high drive, and the ever-present perception that they were hopelessly affected, were grossly apparent:

Case 3 responded when a perceptual distortion was induced by the therapist in the hope that ideovisceral or ideovascular action would change in the patient's fixed awareness of both her ugly ichthyosis and a hopeless social future. This hope has been realised, and she has been well for 4 years.

With the same disease, case 4 was frustrated and felt that his condition held him back from realising his ambitions. The perceptual distortion had only moderate value until he gained enough confidence to redirect his drive by deliberate action. This accomplished, he has enthusiastically been able to auto-induce subjective skin sensations, and his remission has lasted for 2 years.

In case 5, the frustrated husband tended deliberately to look for exacerbations of his eczema. The tense home situation, which caused a continued high-drive state, was emphasised by

his wife's psychosomatic effects. The experience of happier relations with his wife seemed to be crucial in establishing and maintaining the desired perceptual distortion of " no itch ". It also reacted beneficially upon his wife.

In case 6 the use of perceptual distortion was limited, yet it was implicit in that it had been early suggested that weight loss would be of specific benefit. The redirection of drive which occurred seemed to initiate the complete regression of the lesions affecting her vulva and scalp.

Induced perceptual distortion and redirection of high drive into non-frustrating channels are shown in all these cases. We submit that the distortions have induced ideovascular activity, and that this has apparently " allowed " remission. In case 3, however, the perceptual distortion seemed to be predominant whereas redirection of drive was most obvious in case 6. The mechanisms postulated in cases 5 and 6 may be questioned, because both conditions can be caused to regress without overt reference to psychological treatment; but the same cannot be said for the cases of ichthyosis, because in this condition remissions are uncommon.

Treatment by suggestion, leading to resolution of physiological dysfunction, cannot possibly affect the essential organic substrate which predisposes to the disease. Where the psychological component of a disease process is dominant, we have postulated that ideovisceral and ideovascular effects have brought about its activation, and that these effects can be reversed—either directly, by altering the patient's body percept, or indirectly, by redirecting his state of emotional high drive.

The psychological treatment of skin diseases based on this concept makes possible considerable physiological readjustments, and it may explain the success or failure of treatment by a variety of psychological therapeutic approaches.

**Summary**

A mechanism is discussed whereby psychological stresses can produce skin lesions in areas of somatic weakness.

In states of emotional " high drive ", suggestion produces " ideovisceral " and " ideovascular " effects in these susceptible areas.

Experimental evidence for this has led to a method of treatment by inducing perceptual distortion. Cases are described which illustrate the modes of action.

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# OBSERVATIONS ON THE RETINAL BLOOD-VESSELS IN MONOCULAR BLINDNESS

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It is now well known that patients presenting with cerebral vascular disease may be found to have occlusion or stenosis of the carotid artery in the neck. A few of these patients complain of transient or permanent failure of vision in the eye on the side of the diseased carotid; and there is little doubt that this is due to retinal ischæmia, although the way in which it comes about is uncertain. For this reason observations on the retina during the onset of visual symptoms are of particular interest; and in the two cases described here—one with intermittent and the other with permanent monocular blindness—there was direct evidence of retinal embolism.

## First Case

A lorry driver, aged 54, went to his doctor complaining of episodes of tingling and clumsiness in the right hand and arm, but nothing abnormal was found. Blood-pressure during an attack of tingling was 134/88 mm. Hg, pulse was 72 per minute and regular. The pupils were equal and reacted normally. He continued to complain of intermittent symptoms in the right hand and also mentioned to his workmates that his vision was blurred from time to time. It was not clear whether one or both eyes were involved.

On the day of admission at 5 P.M., he was dressing to go out and complained to his wife that his collar seemed tighter than usual. After a struggle he managed to fasten it and bent down to put on his shoes. At that moment he gave a groan and toppled to the floor. For a few seconds he was motionless and appeared to be unconscious, but quickly came round and tried to get up. It was at once apparent that the right arm and leg were weak and clumsy, and although he spoke freely he made many mistakes with words. He managed to explain to his wife that he could not see out of the left eye and kept rubbing it with his left hand. He made no complaint of headache.

A doctor was called and found him anxious and confused; he obeyed simple commands but conversation was rambling. He was unable to name a number of common objects. There was flaccid weakness of the right arm, and the right leg was affected to a lesser degree. Tendon reflexes were diminished on that side and the right plantar response was unobtainable.

These signs were confirmed when he was admitted to hospital at 8 P.M., three hours after the stroke. In addition, the pulsation in the left carotid artery was thought to be less than on the right.

*Ophthalmoscopic Observations*

At 8.30 P.M. the fundi were examined and the vessels in both eyes were normal. The pupils were reactive, and the patient could read newsprint with each eye. Visual acuity was not measured further, and fields were full to confrontation. An

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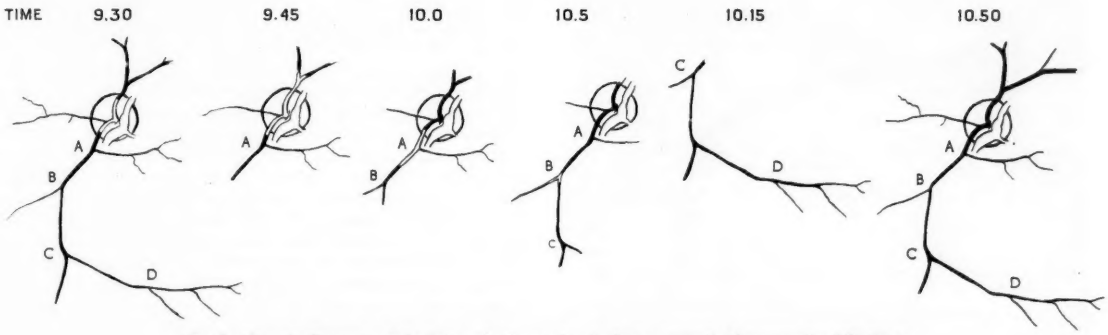


**Fig. 1—Case 1: diagram of the left retinal arteries during an attack of monocular blindness.**

hour later, while the right fundus was again being examined, the patient unexpectedly said: " No, the other side can't see." This was the first indication of visual disturbance since admission. The patient tended to rub the left eye and there was a moderate amount of conjunctival injection. He could discern light, but was now unable to count fingers with the left eye. The left pupil reacted sluggishly to direct light, but consensual reaction was normal. On examination of the retinæ it was noticed that the left was a little paler than the right. On the left side all the vessels were dark blue, and it was difficult to distinguish arteries from veins. Segmentation of the blood-column with slow " streaming " of the flow could be seen in the veins near the disc draining both the upper and lower halves of the retina, but the vessels were of normal calibre. The blood in the arteries was dark and a few areas showed segmentation (clear areas alternating with areas where the cells appeared clumped together), but this was nowhere so obvious as in the veins.

The calibre of the arteries was uniformly a little reduced on the left side. As the central artery emerged from the disc it appeared to be filled with a white substance which extended into its two main branches as far as the edge of the disc. The artery did not collapse or pulsate when digital pressure was applied to the globe. The appearances remained unchanged for about fifteen minutes, and it was then noticed that the white substance was extending further down the lower retinal branch. It had a white granular shining appearance quite different from the clear areas in segmented veins and arteries.

There was a sharp line of demarcation from the blood, and the vessel was not constricted at this point. The blood on the proximal side of the white body was a little darker than on the distal side. The progress of the body down the retinal branch artery was closely observed (see fig. 1). Movement was never rapid or pulsatile, but along the straight stretches of vessel it could easily be discerned. At a bifurcation the white body tended to stick and to break into two sections. When sitting astride a junction in this way, it appeared to distend the arterial wall a little. Over the course of forty-five minutes the body was followed from the disc to a small artery in the neighbourhood of the macula. It diminished considerably in size during this time, as rounded fragments were seen to separate from the main mass and to disappear into the smaller arteries.

At 10.15 the appearance of the disc and the main retinal arteries was once more normal. Arterial calibre was equal on the two sides. The usual colour difference between arteries and veins was apparent (it was not noticed whether this returned suddenly or gradually). The ophthalmic artery pressure (Bailliart ophthalmodynamometer) at this time was: rt. 110/50, lt. 40/?; systemic blood-pressure 165/100 mm. Hg. The retina in the macular area was pale and œdematous and a red spot was visible.

At 10.30 when fragments of the first white body were still visible in the small arteries, a second white body appeared at the disc. Exactly the same sequence of events followed, and the body took the same course down the lower retinal arteries but reached the small arteries in a rather shorter time (thirty-five minutes). The structure of the white body was studied carefully. It had a shining granular appearance and completely filled the artery. A thin irregular red streak possibly composed of red blood-cells was seen on the surface. By 11.5 the vessels were once more normal, but there was considerable retinal œdema with a distinct cherry-red spot. Both eyes had been atropinised, so pupillary reaction could not be tested. Perception of light had disappeared in the left eye.

Recent thrombotic occlusion of the left internal carotid artery was diagnosed, and it was thought justifiable to explore the artery in the neck.

*Operation*

The operation (Mr. A. J. Gunning) began at 11.30 P.M., six and a half hours after the stroke. The skin incision followed the anterior border of the sternomastoid muscle, from the mastoid process to the middle of the neck. The carotid sheath was approached by blunt dissection, during which a number of small veins running transversely were tied and divided. The carotid sheath was incised over the carotid bulb and the common carotid artery and then the proximal inch of the external and internal carotid arteries were dissected free. The internal carotid was larger than usual and was more closely adherent to the sheath than was the external carotid. Pulsation was felt in the common carotid and external carotid arteries, but could not be felt in the proximal inch of the internal carotid, which appeared to be filled with firm material. Beyond that point the artery wall felt soft and there was slight pulsation.

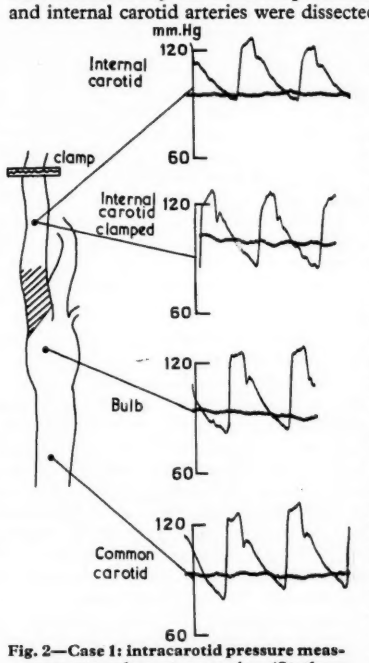


**Fig. 2—Case 1: intracarotid pressure measurements taken at operation (Statham strain-gauge manometer).**

Thick line is E.E.G. lead from left temporal area. Shaded area shows extent of endarterectomy.

Tapes were passed round all three arteries and the blood-pressure was measured in the common carotid, carotid bulb, internal carotid, and external carotid, using a Statham strain-gauge manometer, the artery being punctured

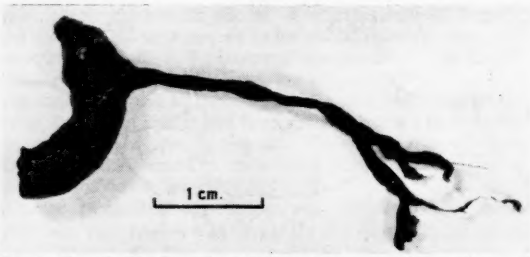


**Fig. 3—Case 1: distal portion of thrombus removed from internal carotid artery at operation, showing the ophthalmic branch.**

with a no. 1 needle. Systolic and diastolic pressures were equal in all three arteries and were the same as the systemic pressure measured by an arm-cuff. The internal carotid artery was then clamped with a Pott's clamp 2 in. above the origin and pressure measurements were taken below the clamp. These were unaltered (fig. 2).

Clamps were then applied to all three vessels, and the carotid bulb and proximal inch of the internal carotid were incised longitudinally. The lumen of the internal carotid was almost full of thrombus. Endarterectomy was performed in the proximal inch of the internal carotid, where the thrombus was firm and appeared to be organised and adherent to the intima. The upper clamp was then released and slight non-pulsatile backflow occurred. A small catheter was passed, but could not be made to go more than an inch up the artery. A corkscrew reamer was then tried, and small quantities of dark red thrombus were removed piecemeal from the cervical portion of the internal carotid. This thrombus appeared fresher than that removed from the endarterectomy site. Eventually, when the reamer reached the base of the skull, a large black recent thrombus was recovered (fig. 3); and this was followed by profuse, pulsatile backflow. The clamps were reapplied and the artery was sutured. At the end of the repair, when clamps were removed good pulsation was present in all parts of the internal carotid. The neck was closed in layers over a small drain.

The operation lasted two hours and the internal carotid was clamped for a total of twenty-five minutes. Just after the clamps were applied the systemic systolic blood-pressure suddenly fell from 130 mm. to 80 mm. Hg. The patient was tipped head-downwards, but no other measures were taken to raise the blood-pressure which rose gradually and spontaneously to 135 mm. over ten minutes. No change was noted in the condition of the patient at this time, nor in the electroencephalographic (E.E.G.) record taken from the left temporal area and monitored continuously on a screen. Intravenous heparin (10,000 units) was given during the period when the artery was clamped and was counteracted by 'Polybrene' (hexadimethrine bromide) before the clamps were released.

*Postoperative Course*

Six hours after the operation the patient was still unconscious, but moved the left arm and leg to painful stimuli. Reflexes were diminished on the right side and the right plantar response was extensor. Blood-pressure was 160/100 mm. Hg, and pulse 80 per minute, regular; both carotid and both superficial temporal pulses were palpable; the retinal arteries appeared normal (ophthalmic artery pressures rt. 125/60, lt. 130/75), and the left disc showed some macular œdema. Lumbar puncture at this time produced clear fluid under normal pressure. The patient was nursed flat in an oxygen tent and was given 90 g. of urea intravenously in 250 ml. of 20% invert sugar in an attempt to reduce cerebral œdema, but there was no apparent change. Anticoagulants (phenindione) were started two days after operation.

For the first week after operation the patient remained abnormally drowsy, and when roused he obviously had profound right hemiplegia, hemianopia, and diminution of sensation on the right side. He was aphasic, making only inarticulate noises, and failed to comprehend simple spoken and written commands. The left retina remained œdematous for three or four days postoperatively and the left pupil reacted sluggishly to light for the same period. The retinal vessels appeared quite normal. Visual acuity could not be tested, but reaction to menace was present with either eye. Seven days after the operation a left carotid angiogram showed the internal carotid and intracranial vessels to be of good calibre. There was no delay in internal carotid circulation compared with external.

At the end of two weeks there was some return of voluntary movement in the right leg and to the upper part of the right arm. The right side of the face and the right hand and forearm were completely paralysed. The hemianopia persisted and appreciation of a painful stimulus was clearly reduced on the right; reflexes were now increased on that side and the plantar response was extensor. The patient could say "yes" or "no" appropriately, recognised his relatives, and carried out simple spoken commands. At this stage he appeared to be recovering slowly from severe hemiplegia, and anticoagulants were continued, the one-stage prothrombin time (Owren's method) being maintained at 14–24% of normal. Erythrocyte-sedimentation rate, hæmoglobin, packed-cell volume, white blood-cell count, and platelet count were all normal.

Despite this treatment, three weeks after the operation swelling of the right calf and foot developed over the course of two or three days. Pitting œdema was present below the knee; the toes and dorsum of the foot were dark blue, but remained warm. Arterial pulsation below the femoral artery was absent on the right. Popliteal venous thrombosis was diagnosed, but over the next two weeks the toes and foot gradually became colder and the toes blacker, while a line of demarcation appeared across the foot and advanced slowly up the leg. Eventually a mid-thigh amputation was performed, and it was found afterwards that both popliteal artery and vein were completely blocked, the arterial block appearing to be the more recent.

Anticoagulants were continued, but within forty-eight hours of the second operation the left foot had become abnormally cold and blue and no arterial pulses could be detected below the femoral artery. Pulsation in the left common carotid and superficial temporal arteries, which had been easily palpable, also disappeared at the same time, and the patient's general condition deteriorated rapidly. There were no cardiac murmurs and the pulse was normal and regular. Although no further changes were seen in the retinal arteries, the hemiplegia once more became complete; the patient became stuporose and finally died in coma five weeks after the operation.

*Necropsy*

Postmortem examination was carried out thirty-six hours after death, and no abnormality was found other than in the cardiovascular system and central nervous system.

The heart was not enlarged and there was no valvular lesion. The left atrium was empty; but the right atrium contained a large antemortem thrombus, the size and shape of which suggested an origin in the inferior vena cava or common iliac veins. The septa were not patent. The aorta appeared normal, having a moderate amount of atheroma. The right femoral artery at the level of the inguinal ligament contained thrombus, but was not completely occluded. The femoral vein and external iliac vein on the right also contained recent thrombus. On the left side the popliteal artery and vein were similarly involved. The right subclavian and carotid vessels were patent and showed only a few patches of atheroma; but on the left side the common carotid, internal carotid, and external carotid were all occluded by antemortem thrombus which extended from the origin of the common carotid as far as the bifurcation of the internal carotid into anterior and middle cerebral arteries.

The left vertebral artery was larger than the right, but both were of good size and free from atheroma. The basilar and posterior cerebral arteries were normal. A large posterior communicating artery was present on the left side, but this artery was absent on the right.

Coronal slices of the brain showed cortical and subcortical softening in the territory of the left middle cerebral artery. In

the parietal lobe there was extensive necrosis and liquefaction of a wedge-shaped area of brain, but in the temporal and frontal lobes the changes were much less distinct (fig. 4). The basal ganglia were not affected.

The middle cerebral artery was patent for most of its course, but was occluded by an antemortem thrombus at an arterial junction in the neighbourhood of the necrotic zone. The artery at this point showed no atheroma.

Histological examination of arteries from many parts of the body showed moderate patchy atheromatous changes, but no evidence of arteritis. The thombus in the branch of the middle cerebral artery appeared to be some weeks old and was in process of organisation. The thrombus in the internal carotid appeared much more recent and was unorganised.

*Histological Examination*

The specimens removed from the carotid artery at operation were of three kinds: (1) a portion of the intima of the artery with attached thrombus from the site of endarterectomy; (2)

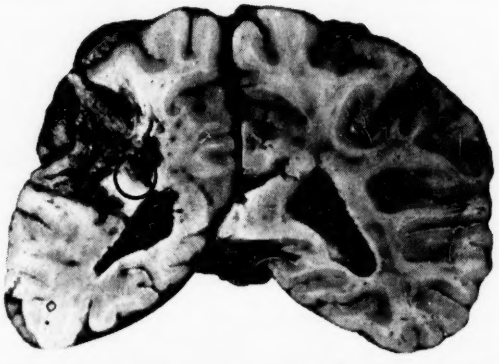

**Fig. 4—Case 1: coronal section of brain through parietal lobes.**
The portion of the artery blocked by thrombus is indicated.

numerous small pieces of dark recent thrombus which were removed piecemeal from the cervical portion of the internal carotid; (3) a larger thrombus forming a cast of the cavernous part of the carotid artery with a smaller branch 3 cm. long joining the main trunk near its distal end (fig. 3). This branch was probably an incomplete cast of the ophthalmic artery and its branches.

The endarterectomy specimen included the intima and a portion of the media with the internal elastic lamina. The lumen was mostly occupied by thrombus. The media contained collagen, elastic tissue, and smooth muscle arranged in a normal manner apart from a few lakes of mucoid material interrupting the elastic laminæ. The intima was thickened and cellular. There was an excess of fibroblasts and metachromatic material on the inner surface. Numerous lipoid-containing macrophages were scattered evenly throughout the intima, and there were a few iron-containing phagocytes. Attached to the intima, but with no definite line of demarcation, was a mass of laminated thrombus in which sheets of red cells alternated with sheets of an amorphous material in which a number of polymorphs were enmeshed (fig. 5). The amorphous material was eosinophilic and appeared reticular in structure. It stained light brown with Mallory's phosphotungstic acid hæmatoxyin and was moderately periodic-acid/Schiff (P.A.S.) positive. Parts of the thrombus near the intima appeared to have become organised. Fibroblasts and capillaries could be seen growing into the thrombus, and there were areas of mucoid and hyaline connective tissue containing lymphocytes, plasma cells, and iron-laden macrophages.

The cast of the upper carotid artery was composed of dark laminated thrombus, but the branch was lighter in colour and the terminal filaments were white, friable, and threadlike (fig. 3). Histological examination of the terminal filaments

**Fig. 5—Case 1: section of laminated thrombus attached to the carotid wall at the site of endarterectomy, stained hæmatoxylin-eosin.**

showed the same reticular ground-substance containing polymorphs. The ground substance again stained with P.A.S., but did not stain for fibrin, except for a thin rim round the periphery. The mass is probably largely composed of agglutinated platelets (fig. 6).

## Second Case

A burly 40-year-old Oxfordshire farmer was sitting having a glass of beer with some friends one evening at nine o'clock

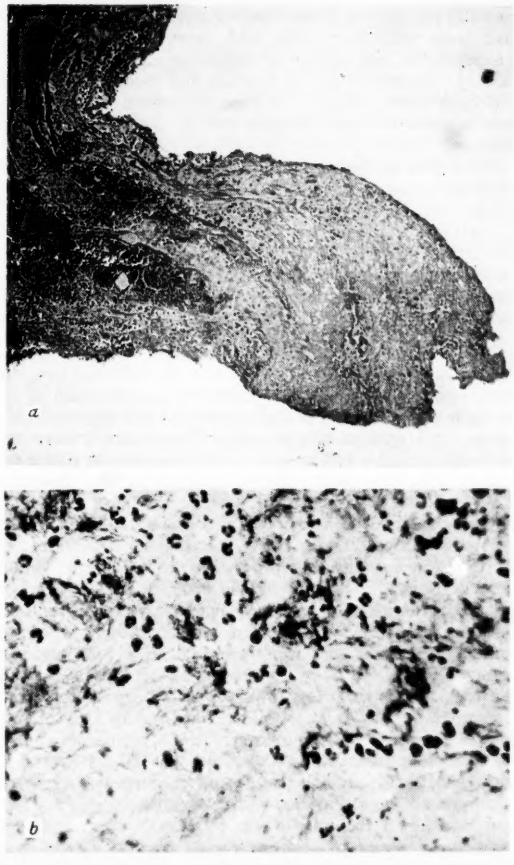


**Fig. 6—Case 1: sections of white terminal filaments from thrombus in the ophthalmic artery (*a*) stained hæmatoxylin-eosin, (*b*) stained phosphotungstic-acid/hæmatoxylin (enlarged view).**

when suddenly he noticed that his vision had become blurred. Thinking this was caused by the smoky atmosphere he rubbed his eyes and found, by closing each eye alternately, that the defect was confined to the right eye, where it seemed as though a number of grey blurred areas were present in all parts of the visual field. On testing his vision further, he was still able to see clearly the face of the proprietor who stood behind the bar across the room. He was a little alarmed but finished his drink, took leave of his friends without mentioning the matter to them, and walked home without difficulty—a distance of about 100 yards. He slept soundly and on waking the following morning found that the vision in the right eye had improved, although a few grey patches were still there. He began his work and later at breakfast was able to read a newspaper with the right eye. Between 9 and 10 A.M. he was walking round the farm when he noticed that the grey patches were growing larger and darker, and by 10.30 A.M. he could see only a chink of light on the temporal side, the rest of the field of the right eye being in darkness. He went to his physician, Dr. G. D. Bolsover, who, finding his blood-pressure to be 220/130 mm. Hg, sent him at once to hospital.

For the past five years the patient had been known to be hypertensive, and eighteen months before the present illness he had complained of a blurred spot in front of the right eye which persisted for three weeks. He was found at that time to have a number of hæmorrhages and exudates in the macular region, and partial retinal venous thrombosis was diagnosed by an ophthalmologist. The left retina also showed hæmorrhages and exudates, and the blood pressure was 220/135 mm. Hg. The urine contained a small quantity of protein and occasional white blood-cells and hyaline casts. Blood-urea was 70 mg. per 100 ml. and an intravenous pyelogram was normal. He had been treated at home with bretylium and later with guanethedine, but control of blood-pressure was never satisfactory. He complained of faintness and weakness on exertion and took fewer tablets than were prescribed. There was no family history of hypertension and no past history of renal disease.

He arrived at the hospital at 3.30 P.M., about eighteen hours after the onset of visual symptoms. Visual acuity was 6/6 in the left eye, and in the right was reduced to finger-counting in a small area in the temporal field. The optic disc was normal; the retinal arteries showed much irregularity both sides; and there was very slight macular œdema on the right. The blood-pressure was 220/140 mm. Hg, but fell to 160/90 mm. Hg following subcutaneous injection of pentolinium.

*Ophthalmoscopic Observations*

The fundi were examined at 11 A.M. the following day, when vision on the right side was restricted to perception of light in the temporal field. The right retina was pale and œdematous, with a red spot at the macula. The retinal arteries were reduced in calibre and were dark, and segments of all the main vessels were obscured by patches of retinal œdema. No blood-flow could be discerned in the lower retinal arteries or in the superior nasal vessel, but sluggish flow was seen in the superior temporal vessel. Every thirty seconds or so a white body appeared at the disc and progressed slowly up the superior temporal vessel. Sometimes the body filled the vessel and moved up it in a jerky fashion synchronous with the heart-beat; at other times the body was smaller and travelled more rapidly, appearing to tumble over and over as it was swept along. The white body was invisible as it traversed patches of œdema along the artery, but reappeared beyond the œdema. It tended to stick at vessel bifurcations and to break into two pieces. Some small retinal arteries near the macula appeared to be entirely filled with white substance. Digital pressure on the eyeball did not collapse any of the arteries at the disc, although the veins emptied at the slightest pressure. On the left side the arteries pulsated on digital pressure in the normal way.

A constant succession of emboli were observed over a period of twenty minutes and some of these were photographed (fig. 7). The emboli then ceased and the blood-flow through the retinal arteries appeared to be at a standstill. Subsequently intravenous heparin treatment was begun, and the blood-pressure was maintained at about 160/100 (lying) with guanethedine. Angiography showed slight narrowing at the origin of the right internal carotid artery; the right and left common carotids and the right and left vertebral arteries were normal throughout their length.

Frequent observations were made over the next three days and similar emboli were seen from time to time by different observers. After three days the eye was completely blind and no more emboli were seen, but a number of small linear hæmorrhages appeared round the disc. Four days after admission the patient complained of numbness of the left hand and arm as far as the shoulder. There was no alteration in pulse or blood-pressure, and the sensation disappeared in fifteen

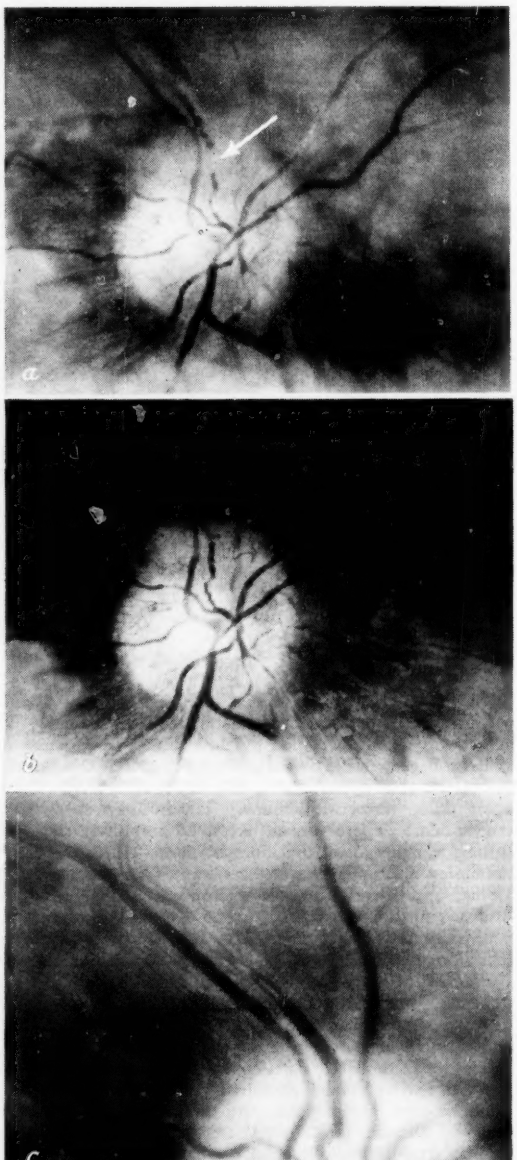


**Fig. 7—Case 2: *a* and *b*, retinal photographs showing the passage of a white embolus through the superior temporal artery (interval of 10 minutes between the two photographs); *c*, same area 3 weeks later.**

minutes. Twelve hours later another such attack occurred, lasting about fifteen minutes; during this attack there was subjective blunting of pinprick over the whole of the left hand and arm, with slight impairment of two-point discrimination. The reflexes were unaltered and the leg and face were not affected. No more retinal emboli were seen.

The condition of the retina showed little change over the next two weeks. The arteries rapidly increased in size, although still obscured in places by œdema, and the retina regained its normal colour. The disc showed increasing pallor, and no vision returned. Two small flame-shaped hæmorrhages appeared near the superior temporal vein after one week. At that time normal arterial pulsations occurred on digital compression of the globe, and the ophthalmic artery diastolic pressures were 70 g. right and left (Bailliart). The systemic blood-pressure was 160/90 mm. Hg.

*Comment*

The principal interest of this case is the observation of repeated embolism of friable white material distal to a thrombotic occlusion of the ophthalmic artery. The visual loss, which was permanent, had been present for eighteen hours before emboli were observed, and it is not suggested that the retinal emboli were the immediate cause of the visual symptoms.

The rapid return of the ophthalmic-artery pressure and retinal-artery calibre to normal suggests that the ophthalmic artery did not undergo thrombosis and recanalisation but may also have been occluded temporarily by friable thrombus or embolus. The period of occlusion, however, was sufficient to cause permanent neuronal damage.

The evidence for thrombus in the carotid artery was less definite than in case 1, but the attacks of left-sided clumsiness and paræsthesiæ were highly suggestive of intermittent ischæmia of the right cerebral cortex.

## Discussion

In most cases where the ophthalmoscopic findings in transient monocular blindness have been reported, the arteries were seen to be reduced in calibre throughout their course, with slowing and segmentation of the blood-flow and retinal pallor. These changes have usually been ascribed to spasm (Harbridge 1906, Bruner 1921). In four reports, however, the findings were rather different and resemble those in the present case 1.

Benson (1894) made three observations on a young man during transient attacks of blindness and saw the inferior temporal artery become bloodless for a distance of four disc diameters. The bloodless segment moved distally sometimes in a jerky fashion synchronous with the heart-beat, and on reaching a vessel bifurcation it suddenly disappeared leaving a normal fundus. One of the patients reported by Mylius (1928) also suffered from fleeting monocular blindness, and photographs of the fundus during a lengthy attack which lasted for three days showed similar white segments of artery. The photographs indicate clearly that the vessel calibre was unaltered in the white area. Recovery from this attack was only partial. Foerster and Guttmann (1933) witnessed an attack of visual loss in the lower field of the right eye in a man of 34 who also had left hemiplegia. The vessels to the upper retina became bloodless for one and a half disc diameters, but blood was present in the distal part of the artery. A non-pulsatile right carotid artery was found at operation.

In these three reports local arterial spasm was suggested as the cause of the attacks. Embolism was thought unlikely because of the relatively short duration and absence of cardiac disease.

Fisher (1959) gave a lucid description of the passage of a white substance through the retinal arteries during an attack of monocular blindness in a patient with carotid stenosis. His observations were very similar to those seen in the present case 1, but his patient could give an accurate account of the visual field loss at different stages of arterial blockage.

A few additional points were made during the present observations:

(*a*) The white substance was quite different in appearance from the small clear areas in a column of stagnant blood showing clumping or segmentation (the "cattle-truck" appearance). Both features were present at the same time and were carefully compared.

(*b*) The arteries at the disc could not be made to collapse by digital pressure on the eyeball when filled with the white substance.

(*c*) The colour of the blood proximal and distal to the white body was different, the redder blood being distal (case 1). This may have been due to collateral supply via the choroidal vessels.

(*d*) Fragments of the white substance were observed to break off and pass towards the smaller arteries. This may explain Fisher's (1959) observation that the white body decreased in volume during transit through the arteries.

The retinal appearances and the removal of thrombus from the ophthalmic artery at operation in case 1 suggest that the visual symptoms were due to intermittent embolisation of the retinal arteries with fresh thrombus composed mainly of platelets and leucocytes. In case 1 the emboli fragmented and passed through the retinal capillaries causing only temporary retinal ischæmia, but in case 2 the ophthalmic artery was blocked for a longer period and irreversible neuronal damage occurred.

If these deductions are correct it seems probable that small friable microemboli are also carried to the cerebral cortex and may be responsible for the transient ischæmic attacks often associated with carotid-artery disease. These attacks are usually ascribed to periods of local vascular insufficiency, precipitated by falls in systemic blood-pressure and failure of collateral flow in the territory of a diseased vessel, but objections can be made to this hypothesis:

(1) Transient attacks have been observed in which no change in systemic blood-pressure occurred throughout (Alajouanine et al. 1960).

(2) Transient attacks may not be reproducible by artificially lowering the blood-pressure (Eastcott et al. 1954).

(3) Transient attacks may affect separate areas of the cortex or the retina at different times, and the retina and the cortex are seldom simultaneously affected.

(4) Transient attacks are rare after carotid ligation when the pressure is low in the upper part of the carotid artery measured directly or by ophthalmodynamometry (Bakay and Sweet 1953, Russell and Cranston 1961).

(5) Transient attacks may be reduced or abolished by anti-coagulants (Fisher 1959).

Multiple friable emboli such as those produced experimentally by arterial injury and composed of platelets (Florey 1925, Zucker 1947) or the similar white emboli described in the cortical vessels after carotid injury (Denny-Brown 1960) would explain most of the points mentioned in the above objections. It might be thought highly unlikely that multiple emboli would repeatedly affect the same area of cortex or retina, but this seems less

improbable if a propagated strand of thrombus can extend from the diseased artery into one of the branches, as was shown to occur in the present cases. Extension of a carotid thrombus into the ophthalmic branch has been previously recorded (Jaensch 1928).

In the present case 1, although a normal lumen was re-established in the affected artery and the operation was technically successful, the patient's disability undoubtedly became worse afterwards. The finding of thrombus at a distal bifurcation of the middle cerebral artery adjacent to a necrotic area of brain suggests that a portion of the carotid thrombus broke off and lodged in the middle cerebral artery as an embolus. Fall in blood-pressure during the operation may also have contributed to cerebral ischæmia, and the dangers of hypotension during occlusion of a cerebral artery have often been emphasised (Meyer and Denny-Brown 1957).

The implications of the embolic hypothesis with regard to surgery are obvious. If a localised source of emboli can be identified it may be removed, or if this is impossible and embolism cannot be controlled by other means, it may even be advisable to ligate the artery. An alternative would be prompt and effective antithrombotic treatment directed primarily against platelets, since platelet deposition is the first step in the formation of an intra-arterial thrombus, and platelet embolism may produce the first symptoms. The coumarol drugs have no action on platelet deposition (Zucker 1947) and were certainly ineffective in case 1. Possibly heparin retards platelet clumping, but the dose required is higher than that usually employed (Solandt and Best 1940).

It is clearly of great importance when planning treatment of an individual case to consider whether arterial embolism or arterial insufficiency is responsible for symptoms, or whether both processes are in operation together. More clinical observations, particularly on patients during attacks of transient cerebral or retinal ischæmia, are urgently required.


### Summary

The retinal blood-vessels were observed in two patients with carotid disease at the onset of monocular blindness, which in one case was transient and in the other permanent.

From the ophthalmoscopic appearances, and from the subsequent discovery of fresh thrombus in the ophthalmic artery in one case, it was deduced that the visual symptoms were due to intermittent embolisation of the retinal arteries with friable thrombus, mostly composed of platelets.


My thanks are due to Mr. E. Allen, of the Oxford Eye Hospital, who took the retinal photographs, and to Sir George Pickering for permission to report these cases and for his valuable criticism and advice.

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## PROPHYLACTIC USE OF INFLUENZA VACCINE IN PATIENTS WITH CHRONIC BRONCHITIS

### A Pilot Trial


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THE acute exacerbations which punctuate the course of chronic bronchitis provide a large part of the winter work of doctors in industrial areas. In Wolverhampton this is true of both general and hospital practice. In the latter instance, indeed, the number of cases admitted in the winter months is often so large that the admission routine is disorganised and emergency measures have to be instituted.

There is evidence that these exacerbations may be "triggered off" by concomitant influenzal infection (Stuart-Harris and Hanley 1957), and the position in this town worsens considerably during an influenza epidemic. It seemed reasonable, therefore, to try to determine whether or not influenza vaccine had any place in the prevention of exacerbation. Concomitantly some other information might be gained particularly with regard to the bacteriology, virology, and pulmonary function of the patients concerned.

### Organisation of Trial

*Clinical Material*

A group of patients living in north-west Wolverhampton and suffering from chronic bronchitis * had been collected and assessed by one of us (L. E. T.) during the spring and summer of 1960. 55 of these patients agreed to take part in the trial.

Patients were placed in one of the following grades:

*Grade I.*—Habitual cough with sputum. Some breathlessness, often only during exacerbations, which are of shortish duration lasting for one or two weeks each year.

*Grade II.*—Capable of doing moderately heavy work, but with exacerbations lasting a month or more. Moderate disability.

*Grade III.*—As above but capable of doing no more than light or sedentary work.†

Those who were incapable of work, breathless at rest or on slight exertion (grade-IV bronchitis), were excluded from the trial. Some work on this type of patient has already been described (Aspin and Howells 1960). No case of tuberculosis with bronchitis was included. 12 patients showed an eosinophilia of over 500 per c.mm. during the quiescent phase of the disease, often with eosinophils in the sputum. These patients were considered to be asthmatics with superimposed chronic bronchitis.

The patients were divided into two groups by random selection, and each patient was given a code number. Those allocated to the vaccine group received 'Flubron' vaccine ($A.A_2$ Asian-Formosa 7000, B. England 5000). The others received physiological saline solution. The injections were given by a member of the nursing staff using a key provided by the statistical adviser. Thus neither of us knew which injection any individual patient had received.

Throughout the trial patients were seen two weeks after inoculation and again at four-weekly intervals by both

* For the purposes of the trial chronic bronchitis has been defined as "a minimum of three years' history of cough with phlegm on most days for at least three months of the year, with added disability of either increasing dyspnœa or an acute exacerbation of respiratory illness on one or more occasions".

† The grading of patients was essentially a clinical one carried out by one of us. The measurements of expiratory peak-flow and indirect breathing capacity (q.v.) roughly coincide with these groups (tables I and II).

TABLE I—DATA ON 26 PATIENTS IN VACCINATED GROUP

| Grade | Sex | Age (yr.) | Duration of symptoms (yr.) | Peak flow (l./min.) | M.B.C. (l./min.) |
|---|---|---|---|---|---|
| I | M | 29 | 4 | 460 | 126 |
| | M | 33 | 11 | 240 | 50 |
| | M | 48 | 25+ | 380 | 94 |
| | M | 50 | 25+ | 340 | 82 |
| | M | 52 | 20 | 310 | 86 |
| | M | 66 | 9 | 280 | 60 |
| | F | 19 | 10 | 420 | 126 |
| | F | 43 | 21 | 300 | 81 |
| | F | 46 | 13 | 275 | 72 |
| | F | 51 | 25+ | 360 | 93 |
| | F | 52 | 19 | 410 | 79 |
| | F | 64 | 10 | 330 | 70 |
| II | M | 57 | 20 | 170 | 26 |
| | M | 57 | 20 | 260 | 48 |
| | M | 58 | 25+ | 280 | 48 |
| | M | 64 | 25+ | 240 | 58 |
| | M | 84 | 10 | 330 | 58 |
| | F | 53 | 12 | 320 | 70 |
| | F | 62 | 10 | 135 | 42 |
| III | M | 47 | 7 | 110 | 32 |
| | M | 48 | 22 | 165 | 36 |
| | M | 61 | 25+ | 155 | 50 |
| | M | 75 | 4 | 130 | 30 |
| | F | 50 | 10 | 270 | 74 |
| | F | 68 | 25+ | 130 | 22 |
| | F | 69 | 25+ | 125 | 20 |

M.B.C. = maximum breathing capacity.

observers. At each interview patients were questioned about cough and sputum, and expiratory peak-flow was recorded.

## Methods and Materials

*Respiratory Function*

The respiratory capacity was estimated by one observer using the Wright peak-flow meter (Wright and McKerrow 1959). After demonstration by one observer, five readings were taken and the mean of the highest three readings was recorded.

The indirect maximum breathing capacity was measured using the Gaensler spirometer (Gaensler 1951, McKerrow et al. 1960). Five measurements were taken of a forced expiration over 0·75 sec. The result read from the scale gave the volume expired in 0·75 sec. multiplied by 40 and expressed in litres per minute. The assumption in the calculation was that a single expiration lasting 0·75 sec. can be regarded as part of a whole sequence of respirations of inspiration and expiration of equal time period which would represent the breathing pattern of an individual doing a maximum breathing capacity by the direct method over a period of, say, 20 sec.

TABLE II—DATA ON 29 CONTROLS

| Grade | Sex | Age (yr.) | Duration of symptoms (yr.) | Peak flow (l./min.) | M.B.C. (l./min.) |
|---|---|---|---|---|---|
| I | M | 28 | 5 | 520* | 154 |
| | M | 39 | 5 | 310 | 70 |
| | M | 44 | 12 | 510* | 124 |
| | M | 44 | 5 | 350 | 65 |
| | M | 49 | 25+ | 420 | 115 |
| | M | 50 | 20 | 420 | 112 |
| | M | 53 | 25+ | 440 | 94 |
| | M | 56 | 20 | 440 | 96 |
| | M | 57 | 15 | 270 | 57 |
| | M | 63 | 10 | 230 | 64 |
| | M | 65 | 6 | 325 | 75 |
| | M | 66 | 5 | 330 | 53 |
| | F | 39 | 10 | 360 | 70 |
| | F | 41 | 5 | 230 | 60 |
| | F | 59 | 4 | 250 | 57 |
| II | M | 41 | 10 | 320 | 100 |
| | M | 44 | 18 | 200 | 46 |
| | M | 59 | 10 | 200 | 48 |
| | M | 61 | 25+ | 180 | 40 |
| | M | 63 | 20 | 200 | 36 |
| | M | 65 | 20 | 160 | 42 |
| | F | 44 | 25+ | 210 | 50 |
| | F | 49 | 25+ | 230 | 50 |
| | F | 65 | 5 | 265 | 61 |
| III | M | 26 | 16 | 110 | 24 |
| | M | 54 | 14 | 120 | 24 |
| | M | 60 | 25+ | 110 | 24 |
| | M | 63 | 25+ | 150 | 30 |
| | F | 50 | 25+ | 70 | N.D. |

M.B.C. = maximum breathing capacity. * Asthmatic. N.D. = not determined.

(Kennedy 1953). Of the five measurements the first two were discarded and the mean of the last three recorded. Although the indirect maximum breathing capacity was measured initially for the purpose of grading it played no part in the measurement of exacerbations. This was because of the difficulty of transporting the bulky apparatus required to the patients' bedside.

*Sputum*

Sputum was expectorated into sterile universal containers. On arrival in the laboratory, gram and Ziehl-Neelsen films were stained. The sputum was then homogenised using 1% pancreatin (Rawlins 1953). It was then inoculated on to blood-agar (aerobically and anaerobically) and also on to chocolate-agar. Cultures were examined after twenty-four and forty-eight hours' incubation.

*Virology*

Complement-fixation tests to all respiratory viruses were done by the standard methods. In each case a rise and subsequent fall in antibody titre was sought.

*Exacerbations*

It was realised that estimation of the efficacy or otherwise of the vaccine therapy would depend largely on the number of exacerbations recorded. Thus it became of crucial importance to record these exacerbations accurately. This was done partly on clinical evidence, but also by measuring the expiratory peak-flow.

TABLE III—DISTRIBUTION BY SEX AND GRADE OF BRONCHITIS OF 26 PATIENTS WHO RECEIVED INFLUENZA VACCINE AND OF 29 CONTROLS

| Group | Sex | Grade | | | Totals |
|---|---|---|---|---|---|
| | | I | II | III | |
| Vaccine .. .. | M | 6 | 5 | 4 | 15 |
| | F | 6 | 2 | 3 | 11 |
| Totals .. | .. | 12 | 7 | 7 | 26 |
| Control .. .. | M | 12 | 6 | 4 | 22 |
| | F | 3 | 3 | 1 | 7 |
| Totals .. | .. | 15 | 9 | 5 | 29 |

All the patients belonged to one practice, which made their assessment and management easier. They were asked to notify their doctor (L. E. T.) if they felt symptoms of a "cold", increase in cough or sputum, dyspnœa, or illness of any other kind. They were examined clinically and their expiratory peak-flow was determined daily. The "baseline" for each patient had already been determined during the summer months. The exacerbations were then recorded as:

*Mild.*—Increase in cough and sputum with a demonstrable fall in peak-flow reading. Duration of attack usually short—one to two weeks. Patient not confined to bed.

*Moderate.*—Increase in cough and sputum with demonstrable fall in peak-flow. Patient confined to bed or house. Duration of attack two to three weeks.

*Severe.*—Troublesome cough with increase in sputum, often with pronounced dyspnœa. Peak-flow recording considerably reduced. Duration four to six weeks.

Sputum was sent to the laboratory and blood was taken for complement-fixation. This was repeated after two or three weeks, and a third specimen was taken at the end of the trial.

It was agreed that where antibiotic therapy was indicated tetracyline should be administered after the initial specimens had been taken.

## Results

*Overall Results*

As table III shows, 26 patients received vaccine, whereas 29 patients received physiological saline. The two groups of patients contained similar proportions of each grade of bronchitis.

Over the whole period of the trial 10 vaccinated patients experienced ten exacerbations, four of which were associated with positive viral complement-fixation (table IV), but

TABLE IV—EXACERBATIONS AND COMPLEMENT-FIXATION (C.F.) REACTIONS IN 26 VACCINATED PATIENTS

| Grade | Sex | Exacerbations | | | | | | Totals | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mild | | Moderate | | Severe | | | |
| | | C.F.− | C.F.+ | C.F.− | C.F.+ | C.F.− | C.F.+ | C.F.− | C.F.+ |
| I | M | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 |
| | F | 3 | 1 | 0 | 0 | 0 | 0 | 3 | 1 |
| II | M | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| | F | 1 | 1* | 0 | 0 | 0 | 0 | 1 | 1 |
| III | M | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | F | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Totals | .. | 5 | 4 | 1 | 0 | 0 | 0 | 6 | 4 |

* Q fever.

in only two of these was the influenza virus involved. Both these patients were taken ill in the first three weeks after inoculation. In the group of patients who received physiological saline 20 experienced twenty-four exacerbations (table v). 11 of these patients experienced thirteen exacerbations with positive viral complement-fixation tests, but in only 9 cases was the influenza virus involved. Two of these exacerbations occurred in the first three weeks after inoculation.

It is generally recognised that three weeks must elapse before inoculation of influenza vaccine can be expected to confer any protection. Thus if the three weeks after inoculation are disregarded the results appear as follows. In the vaccinated group only one exacerbation occurred, and this was not associated with a positive complement-fixation test to any virus. On the other hand in the control group 12 patients experienced exacerbation. In 7 cases the exacerbations were associated with positive complement-fixation to the influenza viruses included in the vaccine (2 patients had positive complement-fixation tests to other viruses, and 3 had negative complement-fixation tests). It is apparent from these results that the vaccine had a real effect (see statistical note).

TABLE V—EXACERBATIONS AND COMPLEMENT-FIXATION (C.F.) IN 29 CONTROLS

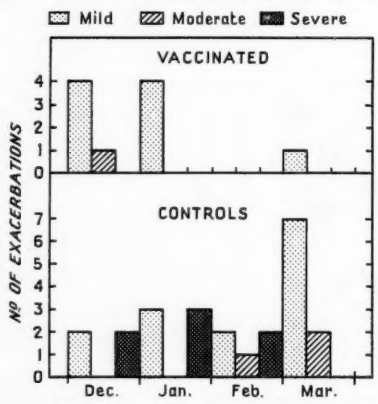
| Grade | Sex | Exacerbations | | | | | | Totals | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mild | | Moderate | | Severe | | | |
| | | C.F.− | C.F.+ | C.F.− | C.F.+ | C.F.− | C.F.+ | C.F.− | C.F.+ |
| I | M | 4 | 4 | 0 | 1 | 0 | 0 | 4 | 5 |
| | F | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| II | M | 3 | 0 | 0 | 0 | 2* | 0 | 5 | 0 |
| | F | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 |
| III | M | 0 | 2 | 0 | 2 | 1 | 2 | 1 | 6 |
| | F | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Totals | .. | 8 | 7 | 0 | 3 | 3 | 3 | 11 | 13 |

* 1 patient died.

1 patient in the control group died during an acute exacerbation. An initial blood specimen for complement-fixation was negative; but it was not possible to repeat the investigation, as in other patients, in order to detect a late rise in antibody level. No deaths occurred in the vaccinated group.

It was necessary to admit 2 patients in the control group to hospital on account of severe bronchospasm. In both cases eosinophilia had been demonstrated beforehand on several occasions. These patients were therefore potential asthmatics even though in 1 case no previous history of dyspnœa had been found. Both patients had positive complement-fixation to influenza A. It was found that during the exacerbation the eosinophilia disappeared only to reappear later. This finding has been reported by other observers (Strang 1960).

Since the grading of exacerbations was essentially clinical, it is not surprising to find that severe exacerbations were commoner in patients whose respiratory function was already severely impaired (grade III). The patients in grade III who received vaccine did not experience severe exacerbation. In the control group, however, 4 patients of the 5 with bronchitis of this severity experienced severe exacerbation. The greatest number of exacerbations in the vaccinated group occurred early in the trial—in late December and early January (see accompanying figure). In the control group, however, they occurred throughout January, February, and March. The influenza outbreak in Wolverhampton was at its peak during these three months.




**Distribution by months of exacerbations in 26 vaccinated patients and 29 controls.**

Table VI shows details of the maximum fall in peak flow brought about by exacerbation. It was found that the time taken for the return to normal of peak-flow measurements coincided with the clinical impressions of return to wellbeing. Whilst the degree of fall in expiratory peak-flow was not necessarily a measure of exacerbation, it nevertheless confirmed the clinical impressions of the observer.

## Statistical Note

NUMBERS AND PERCENTAGES OF PATIENTS WITH EXACERBATIONS AND EVIDENCE OF VIRAL INFECTION

| Data grouping | Control group | | Vaccinated group | | Difference of percentages | Probability ($\chi^2$ or exact) |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| *Exacerbations in period starting three weeks after vaccination:* | | | | | | |
| Positive C.F. to influenza viruses.. .. .. | 7/29 | 24·1 | 0/26 | 0 | −24·1 | 0·008 |
| Negative C.F. to influenza viruses.. .. .. | 5/29 | 17·2 | 1/26 | 3·8 | −13·4 | 0·12 |
| Positive and negative C.F.. . | 12/29 | 41·4 | 1/26 | 3·8 | −37·7 | 0·001 |
| *Exacerbations during first three weeks after vaccination:* | | | | | | |
| Positive C.F. to influenza viruses.. .. .. | 2/29 | 6·9 | 2/26 | 7·7 | + 0·8 | 0·65 |
| Negative C.F. to influenza viruses.. .. .. | 6/29 | 20·7 | 7/26 | 26·9 | + 6·2 | >0·80 |
| Positive and negative C.F. | 8/29 | 27·6 | 9/26 | 34·6 | + 7·0 | >0·70 |

C.F. = complement fixation.

1. The last column gives the probabilities with which the observed and more extreme results would occur if there were no real difference between the exacerbation-rates in the control and vaccinated groups. A value of 0·05 or less is conventionally taken to denote significance, indicative of a real difference between the vaccinated and control group, and thus of a real effect of the vaccine.

2. The probabilities were calculated from $\chi^2$ where the numbers were large enough; otherwise they were calculated exactly.

3. Conclusions here are that the vaccine had a real effect. Reasons: no results were significant in the first three weeks; "positive" exacerbations were significantly fewer in the vaccinated group in the period starting three weeks after vaccination.

TABLE VI—MAXIMUM FALL IN EXPIRATORY PEAK FLOW DURING EXACERBATIONS OF BRONCHITIS

| Grade I | | | Grade II | | | Grade III | | |
|---|---|---|---|---|---|---|---|---|
| Degree of exacerbation | Fall in expiratory peak flow (l/min.) | | Degree of exacerbation | Fall in expiratory peak flow (l./min.) | | Degree of exacerbation | Fall in expiratory peak flow (l./min.) | |
| | Amounts | Difference | | Amounts | Difference | | Amounts | Difference |
| Mild | 240–185 | 55 | Mild | 320– 250 | 70 | Mild | 110– 90 | 20 |
| ,, | 460–380 | 80 | ,, | 280– 230 | 50 | Moderate | 110– 90 | 20 |
| ,, | 410–340 | 70 | ,, | 135–>60 | <75 | ,, | 120–>60 | <60 |
| ,, | 275–230 | 45 | ,, | 200– 130 | 70 | ,, | 120– 85 | 35 |
| ,, | 360–345 | 15 | ,, | 230– 200 | 30 | Severe | 110–>60 | <50 |
| ,, | 300–180 | 220 | ,, | 180– 140 | 40 | ,, | 150–>60 | <90 |
| ,, | 310–260 | 50 | ,, | 180– 115 | 65 | ,, | 70–>60 | <10 |
| ,, | 270–180 | 90 | ,, | 265– 200 | 65 | ,, | 110–>60 | >50 |
| ,, | 530–480 | 50 | Severe | 160–>60 | <100 | .. | .. | .. |
| ,, | 325–250 | 75 | ,, | 200–>60 | <140 | .. | .. | .. |
| ,, | 440–380 | 60 | .. | .. | .. | .. | .. | .. |
| ,, | 440–400 | 40 | .. | .. | .. | .. | .. | .. |
| ,, | 350–315 | 35 | .. | .. | .. | .. | .. | .. |
| Moderate | 230–140 | 90 | .. | .. | .. | .. | .. | .. |
| Severe | 330–110 | 220 | .. | .. | .. | .. | .. | .. |

It was particularly useful in the recording of mild exacerbations where previously the patient's own story was the only evidence; experience has shown that at times this can be confusing. In our experience the peak-flow meter in the hands of a *single observer* can be a useful simple device for recording variations in a patient's condition.

*Bacteriology*

The bacteriological results are shown in table VII. Specimens from patients in exacerbation who had received vaccine did not yield *Hæmophilus influenzæ*. This organism is said by some to be isolated in 80–90% of cases of chronic bronchitis in exacerbation (Mulder et al. 1952, Stuart-Harris et al. 1952, May 1953). It is known that influenza virus can produce epithelial-cell destruction in the bronchiole (Hers 1955), so is it possible that the conditions thereby produced may favour the growth of *H. influenzæ*? This organism was certainly grown with ease from the sputum of patients with exacerbation who had not received the vaccine.

TABLE VII—BACTERIOLOGICAL FINDINGS

| Group | Degree of exacerbation | Grade | *Strep. pneumoniæ* | *H. influenzæ* | *Staph. aureus* | Others | Complement fixation |
|---|---|---|---|---|---|---|---|
| Vaccinated | Mild | I | + | .. | .. | .. | +to influenza A |
| | ,, | I | + | .. | .. | .. | −to all |
| | ,, | I | + | .. | .. | .. | −to all |
| | ,, | I | .. | .. | .. | Yeasts | −to all |
| | ,, | I | + | .. | .. | ,, | +to mumps S & V |
| | ,, | I | + | .. | + | .. | −to all |
| | ,, | II | + | .. | .. | .. | +to Q fever |
| | ,, | II | .. | .. | .. | ,, | +to influenza A |
| | ,, | II | + | .. | .. | .. | −to all |
| | Moderate | III | .. | .. | .. | *Esch. coli* | −to all |
| Controls | Moderate | I | + | + | .. | .. | +to influenza A |
| | Mild | I | + | .. | .. | .. | −to all |
| | ,, | I | .. | .. | .. | Yeasts | +to influenza A |
| | ,, | I | + | .. | .. | .. | +to adenovirus |
| | ,, | I | .. | .. | .. | Fried-lander's bacillus | −to all |
| | ,, | I | + | .. | .. | .. | −to all |
| | Severe | I | .. | .. | .. | .. | +to parainfluenza 1 |
| | Mild | I | .. | + | .. | .. | +to influenza A & B |
| | ,, | I | + | + | .. | .. | −to all |
| | ,, | II | .. | .. | + | .. | −to all |
| | Severe | II | .. | + | .. | .. | −to all |
| | Mild | II | .. | .. | .. | *Esch. coli* | +to parainfl. and Sendai |
| | ,, | II | + | .. | .. | .. | −to all |
| | ,, | II | + | .. | + | .. | −to all |
| | ,, | II | .. | + | .. | .. | −to all |
| | Severe | III | .. | + | .. | .. | −to all |
| | ,, | II | + | .. | + | .. | −to all |
| | Moderate | III | .. | + | .. | .. | +to influenza A |
| | ,, | III | .. | .. | + | .. | +to influenza A |
| | Severe | III | + | + | .. | .. | +to influenza A |
| | ,, | III | + | .. | .. | .. | +to influenza A |
| | ,, | III | + | + | .. | .. | +to mumps S & V |
| | Mild | III | + | .. | .. | .. | +to influenza A |
| | ,, | III | + | .. | .. | .. | +to influenza C |
| | | | | | | | +to influenza B |

S = soluble antigen. V = viral antigen.

*Virology*

It is well known that serological evidence of previous influenzal infection can commonly be found—particularly in older people, many of whom experienced the pandemic of 1918 as well as more recent outbreaks. It was therefore thought advisable to determine the antibody level to influenza viruses in all patients before starting the trial. The levels obtained were comparable in the two groups.

The results of the complement-fixation tests from the blood of patients in exacerbation are shown in table VIII. Whereas over the whole period of the trial there was evidence of influenzal infection in 9 of the controls, this evidence was obtained in only 2 of the vaccinated group. It should be noted that none of the vaccinated patients showed exacerbation after the vaccine could reasonably be expected to have had an effect—i.e., after three weeks had elapsed. A number of other viruses appear to have been the responsible agents in other cases (see table VIII). These findings will be the subject of a further communication. Common-cold viruses were not specifically sought.

## Discussion

Chronic bronchitis has been described as the most important problem in respiratory disease in this country today (Fry 1954, Leese 1956). The most difficult facet of this problem concerns the exacerbations from which all patients suffer. If they could be eliminated, not only would the winter comfort of the patient be improved, but

TABLE VIII—RESULTS OF COMPLEMENT-FIXATION TESTS DURING EXACERBATIONS (IN EACH CASE A RISE AND FALL IN TITRES WAS DEMONSTRATED)

| Group | Degree of exacerbation | Viruses | | | |
|---|---|---|---|---|---|
| | | Influenza A | Influenza B | Asian | Other |
| 4 vaccinated | Mild | 1 | .. | .. | Sendai, parainfluenza 2 |
| | ,, | .. | .. | .. | Q fever |
| | ,, | −1 | .. | .. | Influenza C |
| | ,, | .. | .. | .. | Mumps S & V |
| 11 controls | Mild | 1 | .. | .. | .. |
| | ,, | .. | .. | .. | Adenovirus |
| | ,, | 1 | 1 | .. | |
| | ,, | .. | .. | .. | Parainfluenza 1 and 3, Sendai |
| | ,, | .. | 1 | .. | |
| | ,, | .. | .. | .. | Influenza C |
| | Moderate | 1 | .. | .. | .. |
| | ,, | 1 | .. | .. | |
| | ,, | 1 | .. | .. | .. |
| | Severe | 1 | .. | .. | .. |
| | ,, | 1 | .. | .. | Mumps S & V |
| | ,, | 1 | .. | .. | Parainfluenza |

it seems likely that his life expectancy would be increased, for at each exacerbation there is increased pulmonary destruction (Reid 1957).

The many attempts to control these exacerbations have been chiefly concerned with controlling the bacterial infection by means of antibiotics (e.g., Helm et al. 1954, 1956, May and Oswald 1956, Elmes et al. 1957, Edwards et al. 1957). Only one study has been concerned with the use of influenza vaccine—the Medical Research Council (1959) trial. This involved some 2542 patients attending forty-two chest clinics. The arrangements for collecting information depended on the patients' observations and were " not entirely satisfactory ". No controls were used, and no significant differences were observed between the attack-rate of bronchitis or other respiratory illness in three inoculated groups.

In the present trial, realising from past experience the unreliability of the patients' impressions, we have attempted to measure exacerbation objectively. Not only was the Wright peak-flow meter used, but one observer (his own doctor) who knew the patient well was in attendance whenever exacerbation was anticipated. Further, comparison has been limited to those in whom evidence of influenza infection was unequivocal. Obviously the vaccine used could be expected to confer protection against such infection only after a reasonable interval had elapsed from the time of inoculation. Thus in the first three weeks of the trial the results were similar in the two groups. If this initial period is disregarded none of the vaccinated patients, but 7 of the controls, suffered exacerbation associated with positive complement-fixation tests to the viruses in the vaccine. That in some cases other viruses were involved is not surprising since many of them have been shown capable of producing upper-respiratory illness—e.g., Q fever, adenovirus (Stuart-Harris and Hanley 1957), and parainfluenza 1 and 3 (Tyrell et al. 1959).

Although an influenza epidemic was in progress throughout the winter, the weather was relatively mild and the numbers involved in the trial were small. It would be of interest, therefore, if larger centres could confirm or refute our findings.

If we are right in thinking that the prophylactic use of influenza vaccine greatly reduced the incidence of exacerbation in chronic bronchitis, the vaccine would undoubtedly have a major part to play in the general management of the condition.

**Summary**

26 patients with chronic bronchitis were inoculated with influenza vaccine, and the subsequent course was compared with that in 26 comparable controls who received physiological saline solution.

In the first three weeks after vaccination, exacerbations were equally common in the two groups. During the remainder of the trial none of the 26 vaccinated patients had an exacerbation associated with influenza-virus infection, whereas 7 of the 29 controls had such an exacerbation.

Judged statistically, the vaccine had a real effect.

Our thanks are due to Dr. E. M. Mackay-Scollay for his help with the virus complement-fixation tests; to Pfizer, Ltd., for the supplies of ' Flubron ', antibody estimations, and statistical assistance; to the technical staff of the bacteriology department for incalculable assistance; to the Wolverhampton Hospital Management Committee for allowing us to use the lecture-theatre for seeing patients; to those members of the National Hospital Service Reserve who gave up their free time to help with the hospital sessions; and finally to Mr. R. Paton and his staff for the charts.

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# PREVALENCE OF PARATHYROID INSUFFICIENCY AFTER THYROIDECTOMY

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IN 1890 von Eiselsberg, working in Billroth's clinic in Vienna, established that tetany complicated thyroid operations. The experimental studies of Vassale and Generali (1900) demonstrated the role of the parathyroid glands in the production of the symptom, and by 1906 Erdheim was able clearly to relate the appearance of tetany after thyroidectomy to accidental damage to the parathyroid glands. In those days it was recognised that, in laboratory animals, if only some of the parathyroid glands were damaged, tetany might not appear except at special times such as during growth, pregnancy, or lactation (Morel 1912, Barker 1924).

In patients with a thyroidectomy, partial destruction of the parathyroid glands must be much commoner than a complete loss of all the parathyroid tissue; but the possible effects of a partial parathyroid insufficiency received little attention (Salvesen 1930). Kramer (1936) suggested that a partial parathyroid insufficiency might persist and give rise to symptoms, but generally it was assumed that any surviving parathyroid tissue would hypertrophy to restore parathyroid function to normal, and this was how the spontaneous disappearance of tetany after thyroidectomy was explained. In fact, when some of the parathyroids are removed experimentally the remaining glands do not always hypertrophy (Welsh 1898, Vincent and Jolly 1906), though they may do so (Morel 1912, van Dyke 1959).

The response of the parathyroid glands can be tested by depriving the patient of calcium, and in this way partial or incomplete parathyroid deficiency can be demonstrated (Smith, Davis, and Fourman 1960). For this purpose we have given patients a diet containing only 180 mg. calcium daily, and after 2 days we have added 9 g. of sodium

phytate daily for 3–5 days to diminish the absorption of calcium. In normal persons, the plasma-calcium (plasma-[Ca] ) does not fall with this test, and we have regarded a value below 8·5 mg. per 100 ml. during the test as evidence of deficient parathyroid function. With the aid of the test we set out to ascertain the prevalence of partial parathyroid insufficiency after thyroidectomy and to study its manifestations. To obtain an unselected series of patients for the investigation we made use of a local population survey and the records of two local general practices.

### Populations Studied

*The Vale of Glamorgan*

Prof. A. L. Cochrane, of the Pneumoconiosis Research Unit (Medical Research Council), supplied the names of all persons in a defined area of the Vale of Glamorgan known to have had a thyroidectomy. They had been found in the course of a survey for the prevalence of tuberculosis. The survey was conducted in 1956 and covered 94% of the population (Cochrane et al. 1956). In addition we wrote to the hospitals in which patients from the Vale might have had an operation and this brought to light several patients operated on after 1956. There were altogether thirty-four women and two men, out of a population of 4465 people over the age of 15 years. All of these patients were traced and visited; from one no specimen of blood could be obtained, and another refused to take part in the investigation, leaving thirty-four for analysis.

TABLE I—PLASMA-[Ca] (MG. PER 100 ML.) IN PATIENTS AND CONTROLS

| Age | Controls | | Patients | |
|---|---|---|---|---|
| | No. | Mean | No. | Mean |
| 25–34 | 21 | 9·74 | 12 | 9·72 |
| 35–44 | 21 | 9·71 | 22 | 9·35 |
| 45–54 | 21 | 9·76 | 15 | 9·45 |
| 55– | 19 | 9·67 | 31 | 9·59 |
| All ages | 82 | 9·72 | 80 | 9·52 |
| Standard deviation | | 0·369 | | 0·456 |
| Standard error of mean | | 0·041 | | 0·051 |
| Range | | 8·9–10·8 | | 8·7–10·9 |

P<0·01 for difference of means.

*General Practices in Cardiff*

The records from two large general practices in Cardiff (those of Dr. S. Copp and of Dr. R. Harvard Davis) revealed forty-four women and two men, from a total population of 5329 over the age of 15 years, who had had a thyroidectomy.

All these were visited. For practical reasons, the patients who were later submitted to the test of calcium deprivation were all drawn from this group.

The prevalence of thyroidectomy in the two populations together was 0·8%, with a ratio of 19 females to 1 male. There was an average interval of 10 years between the patients' operations and the investigation.

*Controls*

With the aid of Mr. Peter Oldham of the Pneumoconiosis Research Unit, a hundred control cases were selected by a strictly random process from a census of a Welsh mining valley, the Rhondda fach, made for the unit. The sample was limited to women between the ages of 25 and 65; there were equal numbers of women in each of four 10-year age-groups.

Of this sample, eighty-two women were willing to have blood taken to provide normal standards for comparison with the eighty patients who had had a thyroidectomy.

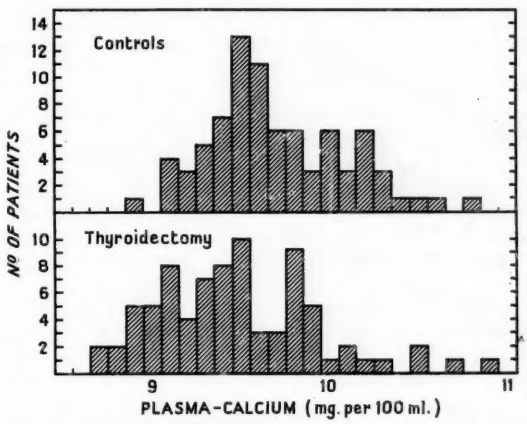


**Fig. 1—Frequency distribution of plasma-[Ca] in controls and in patients with a thyroidectomy.**

### Methods

Calcium in the plasma was determined by the method of Clark and Collip (1925). We found that when plasma or serum was stored the value for the plasma-[Ca] precipitated as oxalate diminished (cf. Salomon et al. 1946). The following plan was therefore adopted for the analysis of the plasma:

Specimens were taken with minimum venous stasis from patients in the Rhondda or the Vale of Glamorgan during the afternoon, brought to the laboratory, and centrifuged the same day. The next day the specific gravity of the plasma was measured to give the protein content, and at 4.30 P.M. the oxalate precipitation was begun, to be completed the following day. On this day a second analysis was begun, to be completed on the day after that. The standard error of one calcium determination was ±0·133 mg. There was no significant difference between the first and the second determinations of the plasma calcium and the mean of the two values has therefore been used.

### Results

*Normal Values for Plasma-[Ca] and Plasma- [P]*

Plasma from eighty-two women was analysed. There was no apparent variation with age (table I). The mean plasma-[Ca] was 9·72 (S.D. ±0·37) mg. per 100 ml. (range 8·9–10·8 mg.), and the mean plasma-[P] was 3·51 (S.D. ±0·75) mg. per 100 ml. (range 2·4–4·7 mg.). Fig. 1 shows the distribution of values. The range of the plasma-

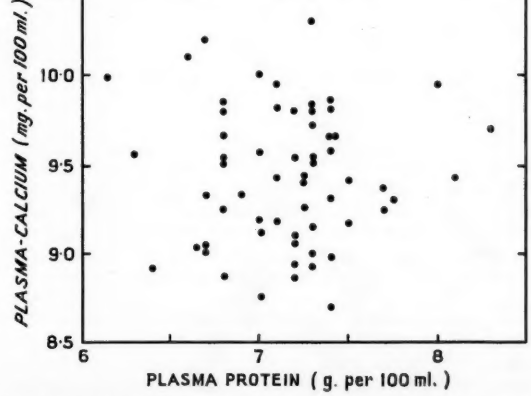


**Fig. 2—Relation between plasma-[Ca] and plasma protein in patients with a thyroidectomy.**

[Ca] was less than that found by Wootton and King (1953), but similar to that found by Keating (1958).

The mean concentration of plasma proteins was 7·0 (S.D. ±0·32) g. per 100 ml. (range 64–8·0 g.).

The plasma-[Ca] was not correlated with the plasma-[P] or with the concentration of plasma proteins (fig. 2).

*Plasma-[Ca] and Plasma-[P] after Thyroidectomy*

In the patients who had had a thyroidectomy, the mean plasma-calcium was 9·52 (S.D. ±0·46) mg. per 100 ml. (range 8·7–10·9 mg.) (table I). The plasma-[P] was estimated in only fourteen patients. The mean value was 3·8 mg. per 100 ml.

Fig. 1 shows the distribution of these values. Only two of the values for the plasma-[Ca] fell below the normal range, and by this criterion the incidence of hypoparathyroidism was under 2%. This figure is similar to that found in many other surveys, which, taken together, give an incidence of 2–5% (Wade 1960). Fig. 1 shows, however, a much greater spread in the plasma-[Ca] in patients after thyroidectomy than in normal persons. The plasma-[Ca] was below 9·3 mg. per 100 ml. in 34% of the patients who had had a thyroidectomy, against 10% of the controls. The low values were not associated with low

TABLE II—PATIENTS WITH A PLASMA-[Ca] LESS THAN 9·3 MG. PER 100 ML.

| — | Number with plasma-[Ca] below 9·3 mg. | Total numbers of patients |
|---|---|---|
| One operation .. .. | 22 (30%) | 73 |
| Multiple operations .. | 4 | 7 |

values for the plasma proteins in individual cases (fig. 2), and the limited observations do not suggest that the low values for the plasma-[Ca] were associated with a rise in the plasma-[P].

*Low Plasma-[Ca] and Type of Operation*

The frequency of plasma-[Ca] values below 9·3 mg. per 100 ml. did not differ significantly whether the operation was a subtotal or a partial thyroidectomy. It was high for the few patients who had had more than one operation (table II).

## Clinical Data

Besides the chemical data described above, the survey provided data on symptoms following thyroidectomy.

One person (R.H.D.) interviewed all the subjects at the time of taking their sample of blood. In doing so he avoided leading questions, though at times he inevitably had to direct a patient's thoughts to certain features. Table III lists the symptoms studied. Although these symptoms were well recognised in hypoparathyroidism many years ago (Biedl 1910, Barker 1924), many of them are nowadays neglected. As a group they are illdefined and it is therefore necessary to elaborate on the meaning attached to some of the terms:

*Abdominal pain.*—Any discomfort or pain, from vague dyspepsia to colic.

*Paræsthesia.*—Usually described as pins-and-needles or tingling, mostly in the fingers and hands, sometimes in the feet, and in one patient in the neck and face. Numbness, usually in the legs, was also included under this heading.

*Mental symptoms.*—A feeling of uneasiness, tension or anxiety, sometimes with attacks of panic, often with depression. Three patients complained of being short-tempered with their families.

*Lethargy.*—A complaint of continually feeling tired, with a disinclination to make any effort or undertake any responsibility. In one instance the patient had hardly been out of the house for 3 years except to do the minimum of shopping. Lethargy was often associated with a neglect of personal appearance. Often the symptoms of depression and lethargy could not be separated.

TABLE III—SYMPTOMS IN PATIENTS GROUPED ACCORDING TO PLASMA-[Ca] FOUND IN SURVEY

| Symptoms | Plasma-[Ca] (per 100 ml.) | | |
|---|---|---|---|
| | Below 9·3 mg. (26 patients) | 9·3–9·8 mg. (31 patients) | Above 9·8 mg. (23 patients) |
| Headaches .. .. .. | 5 (19%) | 1 (3%) | 1 (4%) |
| Abdominal pain .. .. | 7 (27%) | 5 (16%) | 2 (9%) |
| Ectodermal lesions .. | 13 (50%) | 11 (36%) | 5 (22%) |
| Lethargy .. .. .. | 11 (42%) | 6 (19%) | 4 (17%) |
| Mental symptoms .. .. | 18 (66%) | 16 (51%) | 8 (35%) |
| Paræsthesiæ .. .. | 11 (42%) | 11 (36%) | 5 (22%) |
| Symptoms related to menses | 7 (27%) | 9 (29%) | 2 (9%) |

*Ectodermal lesions.*—These included dryness of the skin, thinning of the hair, and brittleness of the nails. One patient had had an eczematous rash a year before the survey was carried out.

Mental symptoms, lethargy, and some other symptoms resembled the normal manifestations of the premenstrual period and were often most prominent at that time. This presented an obvious difficulty of diagnosis from the syndrome of premenstrual tension. Furthermore the symptoms we have described are in any case common in middle-aged women, and in the hypothyroidism that may also follow thyroidectomy. With the idea that patients with a low though not subnormal plasma-[Ca] might have partial parathyroid insufficiency, we decided to compare the findings in three groups of patients, with a plasma-[Ca] below 9·3, between 9·3 and 9·8, and above 9·8 mg. per 100 ml. Table III shows a higher incidence of symptoms, particularly lethargy and paræsthesia, in the patients in the first two groups.

## Calcium Deprivation

There were sixteen patients from Cardiff with a plasma-[Ca] below 9·3 mg. per 100 ml., and thirteen of them consented to have the test. Six other Cardiff patients, four of them with a plasma-[Ca] of 9·3–9·5 mg. per 100 ml., and two with a plasma-[Ca] greater than 9·5 g. also submitted to the test. Of the nineteen tests, twelve were done in the patients' own homes; the other seven were done in hospital.

The results are shown in table IV. The response to the test (low-calcium diet with administration of phytate) was

TABLE IV—RESULTS OF CALCIUM-DEPRIVATION TEST IN PATIENTS WHO HAD HAD THYROIDECTOMY

| Group | | Survey plasma-[Ca] (mg. per 100 ml.) | Initial plasma-[Ca] (mg. per 100 ml.) | Lowest plasma-[Ca] after phytate | Increase in symptoms | Trousseau's sign | Result |
|---|---|---|---|---|---|---|---|
| 1. History of tetany .. | 1 | 8·9 | 9·2 | 7·56 | + | − | + |
| 2. With symptoms | 10 | 9·49 | 8·5 | 8·30 | + | + | + |
| | 13 | 9·16 | 9·15 | 8·13 | + | + | + |
| | 21 | 8·75 | 8·83 | 9·13 | − | − | − |
| | 22 | 8·92 | 9·17 | 8·10 | + | + | + |
| | 23 | 9·53 | 8·6 | 6·7 | + | + | + |
| | 24 | 9·06 | 9·7 | 8·25 | + | − | + |
| | 32 | 9·04 | 8·45 | 7·7 | − | − | + |
| | 35 | 8·98 | 9·5 | 7·1 | + | + | + |
| | 36 | 8·87 | 9·75 | 9·3 | − | − | − |
| | 37 | 9·04 | 9·3 | 7·65 | + | + | + |
| | 42 | 9·19 | 9·05 | 8·43 | − | − | + |
| 3. Without symptoms | 3 | 9·42 | 8·85 | 8·15 | − | − | + |
| | 8 | 10·55 | 8·82 | 8·55 | − | − | − |
| | 14 | 9·10 | 8·94 | 8·75 | − | − | − |
| | 20 | 10·01 | 9·96 | 8·9 | − | − | − |
| | 31 | 9·26 | 9·05 | 8·88 | − | − | − |
| | 65 | 9·33 | 8·8 | 8·8 | − | − | − |
| | 75 | 8·89 | 10·5 | 8·75 | − | − | − |

TABLE V—SYMPTOMS IN THE 11 PATIENTS WITH PARATHYROID INSUFFICIENCY AND THE RESPONSE TO CALCIUM CITRATE IN 9 OF THEM

| Symptom | No. with symptom | Effect of treatment | |
|---|---|---|---|
| | | Treated | Improved |
| Paræsthesiæ | 7 | 7 | 7 |
| Cramp in legs | 5 | 4 | 4 |
| Lethargy | 8 | 7 | 7 |
| Mental symptoms | 8 | 8 | 7 |
| Abdominal pain | 4 | 4 | 4 |
| Syncopal attacks | 1 | 1 | .. |
| Headaches | 3 | 3 | 3 |
| Ectodermal lesions | 5 | 5 | 5 |
| Tightness in throat | 1 | 1 | 1 |
| Exacerbation of symptoms with menses | 3 | 3 | 1 |

considered abnormal if there was a fall in the plasma-[Ca] to below 8·5 mg. per 100 ml. and an aggravation of symptoms.

The patients have been divided into three groups:

1. One with a history of tetany after operation. Her response was abnormal.

2. Eleven with no history of tetany but with some of the symptoms of hypoparathyroidism. In ten the response was abnormal.

3. Seven without symptoms of hypoparathyroidism. These patients had a normal response. As was to be expected, a normal response was found more often among the patients with the higher initial plasma-[Ca] values.

Patients with parathyroid insufficiency as shown by the response to calcium deprivation all had some symptoms, but these were not distinctive. We are at present investigating the effect of treatment on these symptoms; in some cases calcium has had a considerable effect, particularly in patients who were depressed (table v). In a few cases symptoms seemed to bear little relation to the parathyroid insufficiency.

### Discussion

Our survey of patients in Glamorgan who had had a thyroidectomy revealed a high incidence of plasma-[Ca] values in the lower range of normal. Calcium deprivation showed that in many instances these low values were associated with a diminished parathyroid function. Thus twenty-six of the forty-eight Cardiff patients had a plasma-[Ca] of 9.5 mg. per 100 ml. or less. Of these seventeen were tested and eleven had an abnormal response. Therefore at least 24% of the Cardiff patients had some insufficiency of the parathyroid glands.

The reason for this insufficiency is probably that the parathyroid glands are supplied by a small end-artery, usually derived from the inferior thyroid artery. The anatomy was well illustrated by Halsted and Evans (1907) who pointed out that it is in the control of hæmorrhage that the surgeon sacrifices the parathyroid glands.

### Summary

In two defined populations a survey was made of the patients (eighty-two in all) who had had a thyroidectomy. Only one had had tetany. In only two patients was the plasma-calcium (plasma-[Ca]) below normal; but the mean plasma-[Ca] in patients who had had a thyroidectomy was significantly lower than it was in a strictly chosen control group of eighty women.

The prevalence of partial parathyroid insufficiency was demonstrated by means of a low-calcium diet and the administration of phytate. Of the patients who had had thyroidectomy at least 24% showed partial parathyroid insufficiency. This apparently accounted for many minor but disabling symptoms, particularly depression and lassitude. These symptoms could often be cured by administration of calcium.

We are indebted to Prof. Harold Scarborough for his advice and encouragement; to Prof. A. L. Cochrane and members of the M.R.C. Epidemiological Research Unit for their valuable cooperation, and in particular to Mr. Peter Oldham for his advice and help with statistics; and Mr. Ralph Marshall and the department of medical illustration for the charts.

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## THE LOW INCIDENCE OF MYOCARDIAL INFARCTION IN HEPATIC CIRRHOSIS

### A Statistical Artefact?

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THERE is a general impression that alcoholics are less liable to atheroma and its consequences than the population as a whole. Two groups of workers (Grant et al. 1959, Howell and Manion 1960) have recently tried to obtain objective data by studying at necropsy the incidence of myocardial infarction in subjects with portal cirrhosis. In both investigations the frequency of myocardial infarction was about a quarter of that among the total cases examined postmortem. The subjects with cirrhosis were not compared with a control group of necropsy subjects matched for age, sex, and colour. We have therefore reinvestigated this problem using such a control group.

### Subjects and Method

Subjects with cirrhosis of the liver were selected from 23,000 necropsies on the basis of a recorded anatomical diagnosis of portal cirrhosis, Laennec's cirrhosis, nodular cirrhosis, or postnecrotic cirrhosis. The microscopic preparations from all these were rescrutinised, and those not showing definite nodular regeneration and fibrosis were excluded from this investigation. Those subjects with a postmortem diagnosis of cardiac or biliary cirrhosis were also excluded. In this way we obtained a group of 399 subjects with hepatic cirrhosis.

Matched controls were collected in the following way. The 23,000 necropsies were divided into five groups (hospital necropsy nos. 5001–10,000; 10,001–15,000; 15,001–20,000; 20,001–25,000; and 25,001–28,000). For each subject diagnosed as having cirrhosis, a control subject of the same age, sex, and colour was selected at random from the same group of necropsies.

### Results

The mean age of both groups of subjects—those with and those without hepatic cirrhosis—was 52·3 years. Most were white (73%), and males predominated (68%).

Myocardial infarction had been diagnosed in 13 (3%)

of the 399 subjects with portal cirrhosis. Among the 399 controls an anatomical diagnosis of myocardial infarction had been recorded in 43 cases (11%). The frequency of myocardial infarction among the cirrhotic subjects at necropsy was, therefore, only 28% of that among the matched control group. The difference was statistically highly significant ($\chi^2 = 19{\cdot}6$; $P < 0{\cdot}001$).

Of the myocardial infarcts discovered among subjects with cirrhosis, 6 were classified as recent compared with 18 in the control group. This difference was also significant ($\chi^2 = 6{\cdot}2$; $P < 0{\cdot}02$).

### Discussion

The lower incidence of myocardial infarction in necropsy subjects with cirrhosis of the liver observed by Grant et al. (1959) and Howell and Manion (1960) has been confirmed in our study. Previous workers have speculated that hepatic cirrhosis might protect against myocardial infarction by reducing coronary atheroma or by increasing fibrinolysis (Kwaan et al. 1956). Before discussing the biological factors which might be responsible for this relationship, one should question the statistical assumptions underlying investigations based on necropsy data. Mainland (1953) showed that the use of a control necropsy group matched for age, sex, &c., cannot eliminate all statistical bias, and he called attention to the risk of drawing fallacious conclusions from such observations. Cornfield (1959) has pointed out that, even if two lethal diseases have no relationship in a living population, there will nevertheless be a negative association between them in a postmortem study. It is therefore to be expected that the necropsy incidence of myocardial infarction (a fatal disease) would be less among subjects with cirrhosis of the liver (a second fatal disease).

Among our subjects with cirrhosis we also found a lower frequency of extrahepatic cancer, as was noted by previous workers (Gall 1960, Fisher et al. 1960). The incidence of extrahepatic malignant tumours among subjects with cirrhosis was about half that among the controls. Cancers which had metastasised were only about a quarter as frequent (Ruebner et al. 1961). This was comparable in degree with the lower incidence of myocardial infarction among cirrhotics at necropsy. It seems to us that the high mortality of hepatic cirrhosis itself, rather than a lower frequency of myocardial infarction among patients with cirrhosis, is chiefly responsible for the rarity, at necropsy, of myocardial infarction (and of cancer). An inevitable bias of postmortem studies, therefore, seems to have produced an artificial statistical relationship which is invalid in a living population. Evidence has been put forward (Kwaan et al. 1956) that patients with liver disease may have abnormal fibrinolysis —a possible factor in coronary thrombosis. Moreover, cirrhosis of the liver is probably not a single entity, and the effect of postnecrotic cirrhosis on myocardial infarction may differ from that of nutritional cirrhosis. Our negative conclusions, therefore, should not necessarily contra-indicate further study of this problem, both clinically and experimentally.

### Summary

The rarity of myocardial infarction, at necropsy, among cirrhotics has been confirmed. But, because the post-mortem incidence of one lethal disease will be diminished generally among subjects with a second fatal disease, the negative association between hepatic cirrhosis and myocardial infarction in necropsy studies may not be valid in a living population.

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## ALLERGY TO LIGNOCAINE

### A Case-history

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As we have been unable to find any previous reports of true allergy to lignocaine, we record the following case.

A man, then aged 36, first came to the Eastman Dental Hospital in 1954 with gross swelling of the mouth and oropharynx which arose a few hours after injection of 'Xylotox' for conservative dental treatment. Twice in the previous year lesser swellings had followed injections for similar treatment; but when in the Army some years earlier he had had several local-anæsthetic injections without apparent ill effect. He had no dental treatment again until 1961 when he attended this hospital, and it was thought wise to investigate his possible reactions to local anæsthetics. He was a healthy man with no medical or family history of note.

Intradermal skin testing was commenced on the flexor surface of one forearm; control injections of physiological saline and water for injection *B.P.* were used on the other forearm. Tests were carried out with 0·1 ml. of 0·2% solutions of xylotox, 'Xylocaine', L.67,* 'Carbocain', procaine, chloroprocaine, 'Novutox', and nupercaine, both with and without adrenaline.

Except nupercaine, all these substances gave rise to extensive areas of erythema and vesiculation extending from the site of injection within 24 hours, the reactions being far greater with the solutions not containing adrenaline. With xylocaine (Astra-Hewlett Ltd.), the affected area extended over the entire flexor surface of the arm and shoulder, appeared at its maximum 36–48 hours after injection, and did not entirely disappear for nearly 3 weeks. With xylotox (Pharmaceutical Manufacturing Co.), the reaction was even more extensive, and persisted for about the same time.

In addition to lignocaine, xylocaine contains (per 100 ml.) sodium metabisulphite 0·05 g., sodium chloride *B.P.* 0·6 g., adrenaline *B.P.* 0·00125 g., and methyl-hydroxybenzoate 0·1 g. Intradermal skin tests with these substances produced no reaction.

We should like to thank Prof. R. V. Bradlaw for his permission to publish this case, Dr. V. Goldman for his advice on the investigations, and Messrs. Astra-Hewlett for providing some of the special solutions.

* L.67 is a new product, at present on clinical trial, manufactured by Astra A.B. of Sweden.

# Preliminary Communication

## HUMAN SYNOVIAL-CELL CULTURE
## USE OF A NEW METHOD IN A STUDY OF RHEUMATOID ARTHRITIS

THIS paper describes a simple method of dispersing human synovial cells for tissue culture, and gives a preliminary account of the effects on such cultures of serum from patients with rheumatoid arthritis. In principle, the method consists in injection of trypsin into the intact knee-joint of a cadaver or amputated leg, massage of the distended synovial cavity, and withdrawal of the resulting cell suspension for further treatment before culture.

### METHODS

*Dispersal of Synovial Cells*

Attempts to disperse synovial cells by agitation of chopped synovium with trypsin failed to release enough cells for culture. Though outgrowth was obtained by the usual method [1–6] direct from small pieces of synovium, growth was often slow and irregular. Accordingly another attempt to disperse cells was made by injecting various solutions into intact knee-joints.

In view of the concentration of mucopolysaccharide in the intercellular ground-substance,[7] a solution of hyaluronidase was injected, followed by trypsin. Adequate cell suspensions were obtained only in the trypsin solution. Comparative studies showed that the cell yield from trypsin was not increased by pre-treatment with hyaluronidase, although the cells obtained with trypsin alone were sometimes trapped in a mucinous coagulum that could not be easily redispersed.

The following procedure was therefore developed, using knee-joints of subjects aged 60 to 91 years up to 6 hours post mortem, or after amputation for distal gangrene. A needle with stilette was inserted beneath the patella. All solutions were preheated to 35–37°C. The knee-joint was rinsed twice with 50 ml. of Hanks' balanced salt solution and 30–60 ml. trypsin (0·25% in phosphate-saline buffer) was injected and left in situ. After 15 minutes, the distended synovial pouches were massaged until the solution showed opalescence on withdrawal. The trypsin solution was then aspirated, spun at 800–1200 r.p.m. for 10 minutes, and decanted. The cells were resuspended in 20–25 ml. of Hanks' solution, filtered through stainless-steel gauze, counted in a hæmocytometer, spun down in aliquots, and resuspended in culture medium. If a mucinous precipitate formed at this stage, it was spun down, gently agitated with testicular hyaluronidase (100 units per ml. in Hanks' solution) at 37°C for 30 minutes, spun down, washed, resuspended, and counted. Thorough initial rinsing of the joint appeared to reduce the need for this treatment.

*Culture of Cells*

Cultures were established in 'Pyrex' test-tubes and flasks, and in 'Perspex' slides with coverslips for microscopy. Cultures were maintained up to 2 months in Parker's medium 199 [8] enriched by 10–60% of human serum from fasting subjects.

*Study of Rheumatoid Sera*

Sera were prepared from six subjects without joint disease and from six patients with active rheumatoid arthritis ("classical" or "definite", American Rheumatism Association, 1958 [9]; see table I). The arthritic patients had been treated only with salicylate, which was stopped at least 12 hours before blood was taken. Sera were stored at −20°C, thawed, and heated at 56°C for 30 minutes before use. Culture media were composed of 40 or 50% rheumatoid or control serum, 10% reconstituted lyophilised guineapig serum, and medium 199. Aliquots of the cell dispersions were set up in these media to give a cell density of 100,000 to 150,000 per ml., or exposed to the media after a short period of culture in normal media. At least two separate slides were used to study the effects of each medium. Morphological damage was assessed microscopically, and metabolic activity by the colour change of the indicator in the medium due to falling pH; cell outgrowth was

TABLE II—EFFECTS OF RHEUMATOID SERA COMPARED WITH NON-RHEUMATOID SERA

| Experiment | Sera | Age of culture | Effect of rheumatoid sera on culture | New cells at 24 hours |
|---|---|---|---|---|
| 1 | R1 | 3 days | Cell damage and subsequent metabolic inhibition | |
| | C1 | | | .. |
| 2 | R2 | 24 hours | Cell damage and subsequent metabolic inhibition | |
| | C2 | | | .. |
| 3 | R3 | 4 days | Acute cell damage on perfusion and subsequent metabolic inhibition | |
| | C3 | | | .. |
| 4 | R4 | 24 hours | Cell damage | .. |
| | C4 | | | .. |
| 5 | R4 | 0 hours | Inhibition of outgrowth | 23 in 1197 |
| | C4 | | | 58 in 1222 |
| 6 | R5 | 0 hours | Inhibition of outgrowth | 14 in 1200 |
| | C5 | | | 71 in 1200 |
| 7 | R5 | 5 days | Acute cell damage on perfusion | |
| | C5 | | | .. |
| 8 | R5 | 0 hours | Inhibition of outgrowth and cell damage (fig. 4) | 33 in 200 |
| | C5 | | | 52 in 200 |
| 9 | R6 | 0 hours | Inhibition of outgrowth and cell damage | 25 in 400 |
| | C6 | | | 185 in 400 |

TABLE I—SOURCES OF SERA

| Subject | Sex and age | Diagnosis | E.S.R. (mm. in first hour) | Titre of rheumatoid factor [10] | Gammaglobulin (g. per 100 ml.) | Serum-salicylate [11] (mg. per 100 ml.) |
|---|---|---|---|---|---|---|
| Rheumatoid: | | | | | | |
| R1 | M. 72 | Classical | 63 | 1/256 | 2·5 | Not done |
| R2 | M. 54 | Definite | 86 | 1/128 | 2·0 | 0 |
| R3 | F. 69 | " | 65 | 1/256 | 2·6 | 0 |
| R4 | M. 51 | " | 58 | 1/512 | 1·3 | 3·2 |
| R5 | M. 49 | " | 90 | 1/1024 | 1·2 | 3·9 |
| R6 | F. 50 | " | 65 | 1/1024 | 1·8 | 0 |
| Control: | | | | | | |
| C1 | M. 30 | Normal | Not done | <1/16 | 0·8 | Not done |
| C2 | M. 59 | Peptic ulcer | " " | <1/16 | 1·0 | " " |
| C3 | F. 42 | Epilepsy | 6 | <1/16 | Not done | " " |
| C4 | M. 69 | Bronchiectasis | 48 | <1/16 | 1·5 | " " |
| C5 | F. 50 | Peptic ulcer | Not done | <1/16 | 1·1 | " " |
| C6 | M. 63 | Purulent bronchitis | 35 | <1/16 | 1·2 | " " |

E.S.R. = erythrocyte-sedimentation rate.


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9. American Rheumatism Association. *Ann. rheum. Dis.* 1959, **18**, 49.
10. Alexander, R., de Forest, G. K. *Amer. J. Med.* 1954, **16**, 191.
11. Keller, W. J. *Amer. J. clin. Pathol.* 1947, **17**, 415.

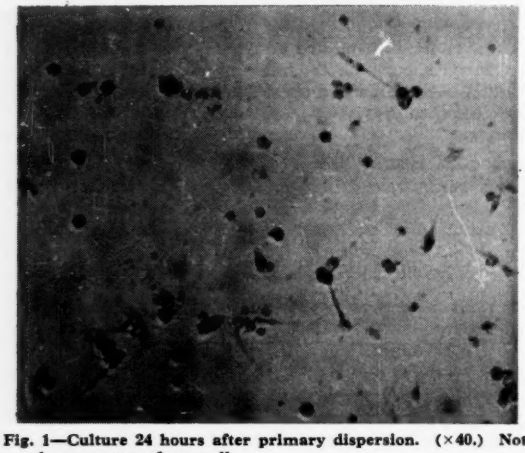


**Fig. 1—Culture 24 hours after primary dispersion. (×40.) Note polar processes of new cells.**

expressed as the proportion of new cells with polar processes about 24 hours after establishing the cultures. The observer was in each case unaware of the identity of the culture.

The early effects of perfusing control and rheumatoid media through established cultures were recorded by serial photomicrographs of groups of cells. Primary cultures were used except in experiments 8 and 9 when subcultures were used four and eight weeks after primary culture. A primary cell dispersion of rhesus-monkey kidney and a subculture of a HeLa cell line were likewise studied.

## RESULTS

### *Cell Culture*

Cultures were readily established by this method. New growth was seen within 24 hours (fig. 1) and developed from the rounded cells of the dispersion with long polar processes and often extensive cytoplasm with many motile mitochondria (figs. 2 and 3). Cultures maintained up to 2 months continued to grow and secrete hyaluronic acid.

### *Study of Rheumatoid Sera*

The effects of each rheumatoid serum were assessed against a non-rheumatoid serum as shown in table II. Metabolic inhibition was the least satisfactory index of damage because pH dropped slowly with the cell concentrations used, and

**Fig. 2—Culture 3 weeks old showing spread of cytoplasm. (×100, N.H. phase contrast.)**

introducing the test media in young cultures often caused uneven washout of cells in different slides, which left the significance of subsequent changes in pH uncertain.

Morphological evidence of cell damage could be expressed only in broad degrees as absent, slight, moderate, or severe, and was therefore assessed with the identity of the preparation unknown to the observer. Synovial cells cultured with rheumatoid serum consistently exhibited greater damage than the control preparations. This was manifest as irregular shrinkage of polar cytoplasmic processes, vesication and varying degrees of cellular dissolution, a lower proportion of new cells with polar processes, and in some instances, an overall reduction in the density of cells, suggesting complete lysis of a proportion of the cells (fig. 4). Counts of the proportion of new cells in the total cell population at 24 hours confirmed the inhibition of outgrowth by rheumatoid sera.

The cultures usually began to recover from these effects

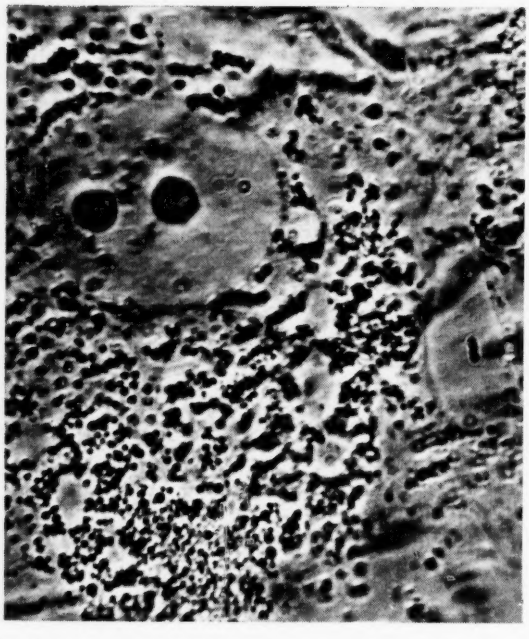


**Fig. 3—Part of single cell (×1000, oil immersion, P.L. phase contrast). Note nucleus, two nucleoli, and many mitochondria.**

after 48 hours, depending upon the initial degree of damage.

Serial observation of young cultures before and after perfusion with control and rheumatoid media showed contraction and partial disruption of cells by rheumatoid media which increased rapidly after 1-1$^1/_2$ hours, and after 24 hours resembled the morphological changes seen in other experiments.

Rheumatoid serum caused no inhibition of outgrowth, metabolic activity, or detectable cell damage in HeLa and monkey-kidney cultures and no acute damage after perfusion of a monkey-kidney culture.

## DISCUSSION

Cell dispersion is a simple reliable means of obtaining connective-tissue cells of synovial origin. In our view, the present method succeeded and the previous attempt failed simply because the synovium consists of only 1–5 layers of cells.[12] Use of the intact knee-joint allowed access to most of these cells, whereas the small amounts of excised synovium contained few cells and much fat and fibrous tissue. Suspension of cells by this method should facilitate

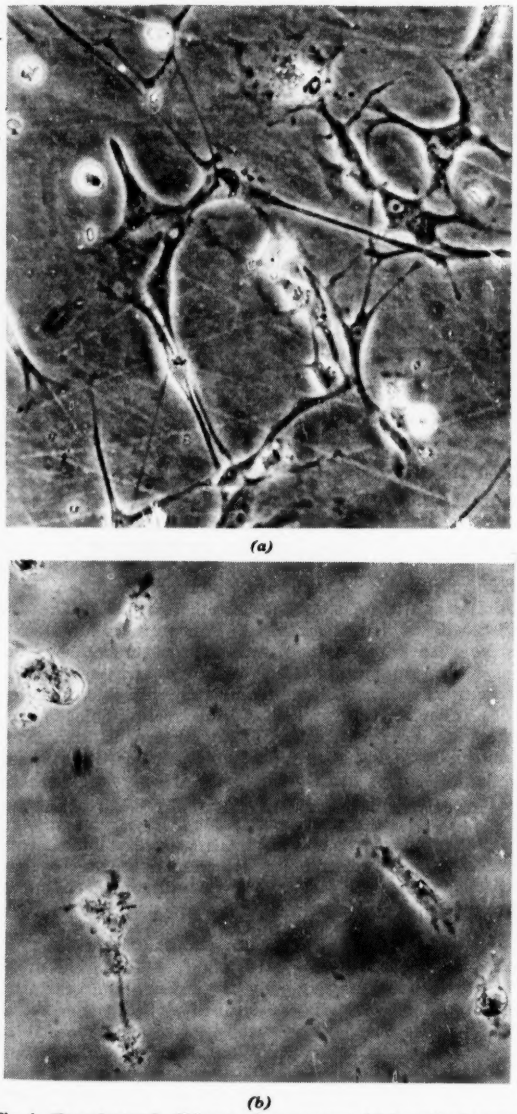
12. Castor, C. W. *Arthr. and Rheum.* 1960, **3**, 140.

quantitative biochemical and immunological study of synovial tissue, and appears equally applicable to vascular endothelial cells.

Contrary to usual experience with adult connective tissue,[13] the cells grow readily even from elderly donors. The early outgrowth allows study before tissue-culture transformation is likely, although this transformation has not yet been noted by us.

Serum from patients with active rheumatoid arthritis appears to damage living human synovial cells in culture. This activity cannot be attributed to salicylate, nor does it seem to be merely a non-specific accompaniment of a raised blood-sedimentation rate or high gammaglobulin (table I). It is not destroyed by heating to 56°C, although the necessity for complement, which was used in the light of unpublished work with explant cultures, needs further clarification. It may be a consequence rather than a cause of arthritis, although it differs from Boake and Lovell's necrotising factor[14] in its resistance to heat, and on present evidence seems more specific than Menkin's necrosin.[15]

13. Paul, J. Cell and Tissue Culture. Edinburgh, 1959; p. 146.



*(a)*

*(b)*

**Fig. 4—Experiment 8. 48 hours after exposure (*a*) to control serum, and (*b*) to rheumatoid serum. (×100, P.L. phase contrast.) Note irregular shrunken cytoplasm in (*b*).**

SUMMARY

A simple method for the dispersal of synovial cells is reported, with a brief description of the noxious effects of rheumatoid serum on cultures of human synovial cells.

We are grateful to Prof. R. R. H. Lovell for his encouragement; to Dr. Gray Anderson for practical help and advice; to Mr. Edgar Rouse, B.SC., for his gift of a phase-contrast microscope; and to the Empire Rheumatism Council for a grant to one of us. Miss Jean Ferguson, B.SC., and our medical colleagues have assisted us materially on many occasions. Mr. E. Matthaei, DIP. OPTICS, and Mr. R. Inglis have provided valuable help with microscopy and photography.

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## Reviews of Books

### Speech Disorders

*Aphasia, Apraxia and Agnosia.* Sir RUSSELL BRAIN, BT., D.M., F.R.C.P., consulting physician to the London Hospital and Maida Vale Hospital for Nervous Diseases. London: Butterworths. 1961. Pp. 182. 42*s*.

SINCE Nielsen's book *Agnosia, Apraxia, Aphasia* went out of print, there has been need for an account not only of aphasia but also of the penumbra of related disorders of symbolising activities such as the agnosias and apraxias. Sir Russell Brain's book is described as an enlargement of his article in Kinnier Wilson's *Neurology*: but it is more than that. It gives a historical and critical review of the subject, and assesses current and past explanations for the clinical observations, as well as mentioning some of the wider area of communication theory which adjoins the territory of speech and aphasia. It is an excellent introduction to the subject and will be widely read. Its main title may mistakenly suggest that it is concerned with speech therapy; and there are fewer case-histories than might be expected when interpretation of the data from the clinical case is especially important. We warmly commend the book to neurologists and psychologists.

### Traumatic Aphasia

W. RITCHIE RUSSELL, M.D., D.SC., F.R.C.P., director, department of neurology, United Oxford Hospitals; M.L.E. ESPIR, M.B., M.R.C.P., consultant neurologist, Leicester Group of Hospitals. London: Oxford University Press. 1961. Pp. 171. 38*s*.

THE subject of speech and its disorders may suffer from too rigid classification, little related to demonstrable anatomical or physiological evidence. It is, therefore, very susceptible to semantic obscurity. But this book suffers from no such defects: it is a straightforward description of speech function in modern terms, drawn from a careful study of 916 patients with penetrating wounds of the brain. Earlier work is cited, but no time is wasted in fruitless attempts to reconcile theories based on different premises or on insupportable assumptions. The links between speech, memory, and other mental faculties are carefully considered. The authors find evidence for certain broad types of speech disturbance after small wounds. The central type disturbs all aspects of speech and causes mental confusion. At the periphery of the "speech scaffolding" individual functions may be particularly disrupted. Thus, posterior parietal wounds cause alexia and severe intellectual loss; wounds posterior to the upper third of the dominant sensory cortex may show a severe disorder of writing; those in the

lower part of the Rolandic area cause motor aphasia. Wounds involving the fornix-hippocampal system in the dominant hemisphere tend to produce long post-traumatic amnesia and impairment of recent memory. Recovery is impaired if the main commissures are damaged. Damage to the pulvinar of the thalamus may silence old memories. Left-sided cerebral dominance is almost invariable in right-handed persons, and commoner in left-handed persons than is right cerebral dominance. There is no evidence from this series that left-handed individuals are apt to use both cerebral hemispheres for speech.

For the specialised rather than the general reader, this book is almost obligatory for anyone interested in cerebral function: it may well become a classic.

### Bleeding Syndromes

OSCAR D. RATNOFF, M.D., associate professor of medicine, Western Reserve University School of Medicine, Cleveland. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961. Pp. 287. 68*s*.

THIS book is chiefly concerned with the clinical features of bleeding syndromes, their signs and symptoms, the age-groups affected, their diagnosis, prognosis, and treatment. Laboratory procedures are taken into account, since accurate diagnosis of these syndromes depends on these tests and their correct interpretation; but details of technique are not included. Within these limits, the account is comprehensive, and covers every syndrome for which a reasonable case has been established, so that most of the less common syndromes find a place—for example, the purpuras associated with dysproteinæmia, the Hageman trait, and the Ehlers-Danlos syndrome. The descriptions are up to date and the results of recent research are mentioned whenever they have a clinical application. Some useful tables are provided, such as the one summarising the results of laboratory tests in the different syndromes and another giving a tentative classification of the causes of thrombocytopenia.

The clinical descriptions are based on the author's large experience. He notes the extraordinary size of hæmatomas in hæmophilia, the greater frequency of cerebral hæmorrhage in thrombocytopenia than in hæmophilia, and the existence of a harmless ecchymotic purpura of women's legs known as "simple" purpura because all the tests of hæmostatic function are normal. The recommended treatment follows accepted ideas for the most part, but not many will agree with the advocacy of joint aspiration for hæmophilic hæmarthrosis. There is a fair discussion of the various views on the management of thrombocytopenic purpura.

This book will be useful to the general physician who wants to know more about bleeding syndromes than can be found in the regular textbooks, but who does not wish to be immersed in laboratory details. There is a good bibliography and, at each chapter end, a few selected references.

### Malformations of the Face

D. GREER WALKER, M.D., M.DENT.SC., F.D.S. R.C.S., consultant dental surgeon, Middlesex Hospital, London. Edinburgh: E. & S. Livingstone. 1961. Pp. 202. 37*s*. 6*d*.

THE title gives a false impression, for this book is in no sense a textbook of congenital facial anomalies (many of the common malformations, such as hare lip, cleft palate, ptosis, or epicanthal folds are not discussed at all); nor is treatment mentioned. The author has taken as his starting point the morphology of certain established lesions and made a detailed analysis "in the conviction that common basic principles should be sought in considering the identity, ætiology and mechanism of production of congenital anomalies wherever they appear". The lesions selected include some that are very rare, and they are grouped under four chapter headings: Variations in the Position of the Orbit deals with hypertelorism and conditions in which the eyes are at different levels; The Plasticity of the Cranio-facial Structures is mainly concerned with those malformations of mandible and skull which may be due to faulty intrauterine posture; An Environmental Hazard of Pregnancy is subtitled "intra-uterine necrosis" and discusses a wide range of lesions, such as maldevelopment or absence of the ears, unusual facial clefts, ring constructions and amputations of limbs or digits; Hazards of Heritage concerns atavism, the Treacher-Collins syndrome, and anomalies of the neck and shoulder.

The book is largely an intellectual exercise on the part of Mr. Greer Walker, who gives as his first reason for writing it that he is able "to unravel his own thoughts and clarify what is often a long and complex experience". But this process of unravelling does not make for easy reading; the writing is discursive, there are digressions that seem hardly relevant, and it is often difficult to follow the thread of his argument. This is a pity, for there are many points of interest and, thoroughly edited, the material would provide four valuable essays on different aspects of the problem. Retrospective deduction of basic causes from end-results is always highly speculative and, inevitably perhaps, firm conclusions are rarely reached.

This book appears at a time when the techniques of chromosome analysis and other genetic tools are adding weekly to our knowledge of congenital abnormalities. Since it was written, there has been a great resurgence of interest in this subject, and in the laboratories more and more information is accumulating about the basic processes involved. The day of philosophical discussion and deductive rationalisation is passing, and this book may well be the last of its kind.

### Biological Effects of Freezing and Supercooling

*Monographs of the Physiological Society*, no. 9. AUDREY U. SMITH, M.B., D.SC., National Institute for Medical Research, Mill Hill, London. London: Edward Arnold. 1961. Pp. 462. 55*s*.

THE monographs of the Physiological Society traditionally deal with a subject of general interest that needs surveying and are written by one of the leaders in the field: this is no exception. As A. S. Parkes points out in a foreword, no coherent, detailed, and authoritative account has been given of the biological effects of freezing and supercooling by a single author for 21 years, and these years have seen dramatic progress. Dr. Smith is well known for her share in the discovery that glycerin protects spermatozoa against damage by freezing, and for applying this discovery to the preservation of human red cells. The storage of glycerin-treated red cells at low temperature is now almost a routine in the preservation of rare blood specimens for grouping, and it has already become a possible method for prolonged storage of blood for transfusion.

This book also discusses the many other problems of freezing and thawing of biological material. This work has now reached a stage where whole animals, such as hamsters, can be supercooled and resuscitated. It will be new to many readers that Arctic fish living at sub-zero temperatures are able to survive because they are supercooled; and the freezing-point of their plasma is lowered by the doubling of its osmotic strength, so that temperatures well below freezing-point are partly offset by the lowered plasma freezing-point.

There are chapters on the effects of freezing and thawing on spermatozoa, microorganisms, tissue cultures, embryos, and poikilothermic animals and mammals, as well as fundamental discussions on the effects of lowered temperature on water and physiological media. This well-illustrated monograph and its large collection of references will become a standard work.

**The Kidney** (2nd ed. London: J. & A. Churchill. 1961. Pp. 374. 50*s*.)—This second edition of Prof. H. E. de Wardener's book, coming only three years after the first, illustrates the success with which it has fulfilled its objective of helping students and "others who wish to know more about the subject". Professor de Wardener has included some account of renal-artery stenosis, counter-currentry, autoimmunity, and erythropoietin; but the revision goes far beyond the addition of new sections, and there are alterations and minor additions in many chapters. The references for further reading are well chosen. This is a good and useful book.

THE LANCET

LONDON 30 DECEMBER 1961

## Parathyroid Insufficiency

IN 1944 a young woman, aged 28, had her thyroid removed on account of nodular goitre. After the operation she had slight cramps and paræsthesiæ which were easily controlled with calcium. In 1953 she was admitted to hospital for the investigation of convulsions and papillœdema, and in 1955 she was blind with cataract —all the result of chronic hypoparathyroidism.

This patient was shown at a staff round, and a surgeon with a special interest in thyroidectomy was led to wonder how often this sort of thing happened and reviewed his cases. He found, as others had before, that the incidence of frank parathyroid insufficiency after thyroidectomy is about 2%.[1] But in Cardiff, with its Medical Research Council Epidemiological Research Unit, follow-up studies on hospital populations are regarded with reserve. Accordingly, the surgeon and a general practitioner enlisted the aid of a metabolician, and together they went to the Epidemiological Research Unit. Their subsequent findings are reported in this issue.

Most surgeons, and for that matter physicians too, recognise hypoparathyroidism by the appearance of tetany, and many have regarded the disappearance of tetany as betokening cure. Others rely on determinations of the serum-calcium to assess parathyroid function after thyroidectomy; but they do not take into account the possibility of spontaneous variations in the plasma [Ca] of patients with hypoparathyroidism. The parathyroid glands normally respond to a fall in the plasma [$Ca^{++}$] (concentration of ionised calcium) by increasing their secretion; the hormone releases calcium from bone and restores the plasma [$Ca^{++}$] to normal. Hypoparathyroidism may be defined as a failure of the parathyroid glands to sustain a normal plasma [$Ca^{++}$] either naturally or when deliberate efforts are made to reduce it. This strict definition has not been followed in the past, when estimates of the incidence of hypoparathyroidism after thyroidectomy varied from less than 1% to 10%.[2] This discrepancy may be due partly to variations in the length and the thoroughness of follow-up. The plasma [Ca] must be measured at least once routinely after thyroidectomy. Hypoparathyroidism may be latent for many years, appearing only when there is a special demand on the parathyroid function, as with pregnancy and lactation or (for some unexplained reason) at the menopause. The diagnosis is not difficult when the symptoms include tetany, but often they do not. The patient may come to the dermatologist with rashes, particularly eczema and impetigo herpetiformis, alopecia, and nail changes,[3] to the gastroenterologist with abdominal pains,[4] to the physiotherapist with a frozen shoulder, to the ophthalmologist with cataracts,[5] to the neurologist with fits and papillœdema,[6] to the laryngologist with attacks of crowing, or to the psychiatrist with an anxiety state or a depressive neurosis.[7] Or she may come to none of these specialists but remain a constant visitor to her doctor's surgery complaining of little other than lassitude and of never having felt well since her operation. The Cardiff study (see p. 1432) suggests that such cases may be commoner than has been supposed.

In this study, of 82 patients who had undergone thyroidectomy none was found to have frank hypoparathyroidism; but when the parathyroid function was tested by calcium deprivation, 24% were found to be unable to maintain a normal plasma [Ca]. Some of these had had transient tetany after their operation. All had banal symptoms which would ordinarily be classed as neurotic or depressive, and the authors imply that these symptoms improved with calcium.

The Cardiff workers seem to have defined a condition of partial parathyroid insufficiency. Partial deficiencies of thyroid, adrenal, and pituitary secretion are recognised in man, and in animals the effects of partial parathyroid insufficiency have already been described: in dogs, as in the Cardiff patients, the most constant symptom was melancholia.[8] The main difficulty in accepting from the Cardiff work the reality of partial parathyroid insufficiency is that the patients' plasma [Ca] was within the normal range, though near the lower limit. The question arises whether it is the level of calcium in the circulating fluids or the level within the cells (particularly cells of the nervous system) that determines the symptoms. The observations of the Cardiff group are indirectly supported by certain psychiatric investigations. BARRETT,[9] in a study of psychosis associated with tetany, mentioned a mood of sadness and fear. FÜNFGELD[10] found that tetany, latent or overt, was commonly accompanied by psychiatric disturbances. He later emphasised that a long interval—as long as nineteen years—might elapse between thyroidectomy and the appearance of symptoms.[11] HOWARD and ZIEGLER[12] and PROKOP[13] found an excessive incidence of depression among patients who had been submitted to thyroidectomy. PROKOP's explanation was that thyroidectomy was often mistakenly undertaken for psychiatric disorders. No doubt this is sometimes so; but the possibility must now be considered that it is the thyroidectomy, with the incidental parathyroid damage, which produces the mental changes.

Surgeons may not readily agree that thyroidectomy by the modern technique, in which the posterior

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11. Fünfgeld, E. Die tetanischen Erkrankungen der Erwachsenen. Leipzig, 1943.
12. Howard, M. Q., Ziegler, L. H. *Amer. J. Psychiat.* 1942, **98**, 745.
13. Prokop, H. *Wien. med. Wschr.* 1958, **108**, 851.

portion of the gland is left intact, can result in such a high incidence of parathyroid damage. The answer must no doubt be sought in the blood-supply of the glandules:

"A special tiny parathyroid artery supplies the gland in every case. This artery may arise from one of the glandular, the muscular, or the œsophageal branches of the inferior thyroid artery, but wherever its origin, it can be seen definitely to supply the parathyroid gland and it alone. Injections have never demonstrated more than one parathyroid vessel proper. In practically every case the lower parathyroid artery came from a prominent branch of the inferior thyroid artery. The upper parathyroid gland invariably has a short artery of supply which may arise from one of the main branches of the inferior thyroid or from an anastomosing ramus joining the superior and inferior thyroid arteries. Most often the angle at which the parathyroid vessel came off from its parent trunk suggested that its blood stream was usually from the inferior source." [14]

The inferior thyroid artery is often ligated during thyroidectomy. An alternative procedure involving hæmostasis beneath the capsule of the thyroid gland also endangers the blood-supply of the glandules.[15] As HALSTED [14] pointed out, it is in controlling hæmostasis that the surgeon sacrifices the parathyroid glands. In view of the dangers it seems inadvisable to identify the glandules during thyroid operations—and in operations for the removal of a parathyroid adenoma—since the dissection may lead to the parathyroid insufficiency which these precautions are designed to avoid. Does treatment of thyrotoxicosis with radio-iodine endanger parathyroid function in the same way? Experimental evidence [16] suggests that it may.

## Barrier Function of Lymph-glands

WE owe to VIRCHOW [17] the first precise formulation of the hypothesis that lymph-glands act as defensive barriers. He pointed out that in a lymph-gland "the elements lie crowded together like the particles in a charcoal filter, so that the lymph trickles out on the other side in a more or less purified state". He supported his view with a section of an axillary lymph-gland from a soldier whose arm had been tattooed with cinnabar nearly fifty years previously (in the tattooing, cinnabar was rubbed into skin pricks):

". . . in the rubbing a certain number of the particles find their way into the lymphatic vessels, are carried along in spite of their heaviness by the current of lymph, and reach the nearest lymphatic glands, where they are separated by filtration. We never find that any particles are conveyed beyond the lymphatic glands and make their way to more distant points, so that they deposit themselves in any way in the parenchyma of internal organs. No, the mass always settles in the nearest group of glands."

The barrier hypothesis was rapidly accepted, since the structure of the lymph sinuses seemed to lend itself so readily to filtering out particulate matter. But how effective is this filter? DRINKER et al.[18] devised experiments to test the filtering efficiency of an individual lymph-gland for bacteria. They perfused a gland with hæmolytic streptococci through the afferent lymph-vessels and collected the fluid from the efferent vessel. Filtration proved to be 99% complete—i.e., only 1% of the perfused bacteria passed through the gland and was found in the efferent lymph. It might be expected that if the thoracic duct and the right lymph-duct were tied bacteria would not reach the blood. But sometimes they do—perhaps because lymph enters the blood through other lymphatic-venous communications in the abdomen, or owing to migration, into the blood-capillaries of the lymph-gland, of phagocytes which have ingested the bacteria.

Apparently, therefore, lymph-glands exercise a very appreciable barrier action against inanimate particles and bacteria. With viruses the position is radically different, as was first shown by YOFFEY and SULLIVAN.[19] They found in rabbits that from a focus of infection in the nose vaccinia virus reached the cervical lymph-gland, proliferated there, and then was discharged from the gland in a steady stream. This cytotropic virus was contained in the lymphocytes which were continually leaving the gland and entering the blood, in which they were rapidly carried all over the body. Thus in the case of viruses which can proliferate in lymph-glands, these glands not only exert no barrier action but constitute a perfect mechanism for quickly disseminating virus throughout the body. Earlier attempts to detect poliomyelitis virus in cervical or thoracic duct lymph were unsuccessful. But in view of the findings of BURROWS [20] and the subsequent demonstration of viræmia in poliomyelitis, with the virus apparently contained in the leucocytes [21]—it seems probable that this neurotropic virus is disseminated in the same way.

Further doubts about the efficiency of the lymph-glands as barriers have been introduced by PRESSMAN and SIMON.[22] Inserting a syringe needle into a cervical gland in a dog, they injected first one or two millilitres of saline solution, and immediately afterwards air, "using only moderate digital pressure upon the syringe". The veins leaving the gland, and even the internal jugular vein, became filled by air, as did the efferent lymph-channels from the lower pole of the lymph-gland. PRESSMAN and SIMON reject the possibility that the needle in the lymph-gland might have directly entered the vein, and believe that the actual site of injection is a lymph sinus. They infer that the gland contains numerous lymphaticovenous communications between the lymph sinuses and the veins. This claim has such far-reaching implications that the work should be repeated both in the dog and in other species. It is important, too, to devise a technique for investigating the movement of liquids and particles.

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# Annotations

## TREATMENT OF PULMONARY EMBOLISM

MASSIVE pulmonary embolism is usually followed immediately by a sharp fall in cardiac output; and the patient may die almost instantaneously, presumably owing to ventricular fibrillation or arrest. Of 100 fatal cases reviewed by Gorham [1] death took place in under ten minutes in 41, and in under two hours in altogether 66. This series covers the years 1934–56, and with modern conservative treatment the proportion of deaths more than two hours after the onset would be expected to be lower. Patients who survive the first few hours have an excellent chance of recovering under treatment with oxygen, heparin, digitalis, and pressor amines—these last to raise aortic pressure and thus ensure adequate coronary flow. A series of 54 cases of pulmonary embolism reported by Barritt and Jordan [2] included 14 of massive embolism; and all 14 patients recovered, though some required infusions of L-noradrenaline or other pressor agents for several hours.

The operation of immediate embolectomy, originally conceived by Trendelenburg, has occasionally been successful [3]; but it is hazardous and should probably not be undertaken unless the heart has stopped beating effectively and the patient will otherwise die. On the other hand there seems to be a place for *planned* surgical relief of massive embolism in selected cases where life or lung function are endangered. Allison et al.[4] removed large adherent clots from both pulmonary arteries with forceps in a patient whose circulation was temporarily interrupted after surface cooling. In another case Cooley et al.[5] induced a cardiopulmonary bypass with a pump oxygenator. The main indication for operation is increasing heart-failure. Assessment calls for considerable skill on the part of surgeon and physician. A falling blood-pressure is the clearest evidence of deterioration; but knowledge of arterial oxygen saturation and arterial end-alveolar $pCO_2$ gradients [6] may prove helpful; and these estimations might be facilitated by an indwelling arterial cannula.

## CLUSTER HEADACHES

THE term " cluster headaches " was coined by Kunkle et al.[7] to describe a form of migraine in which the headaches occur in groups with free intervals of weeks or months. The headache is felt around the orbit, is always on the same side, and is accompanied by lacrimation, redness of the conjunctiva, nasal congestion, flushing of the face, and often palpable thickening of the temporal artery. Horner's syndrome is sometimes found on the affected side. The headache, although briefer—sometimes it lasts minutes only—is much more severe than in the usual migraine; and while the cluster lasts it is often extremely regular in its daily time of onset.

Previously this syndrome had long been recognised under various other names: Wilfred Harris's [8] " ciliary (migrainous) neuralgia " is one of the earliest descriptions. In 1939 Horton [9] suggested that it was due to histamine sensitisation and that a course of histamine desensitisation should help in treatment. Unfortunately successes with this method have been few; and parasympathetic denervation (greater superficial petrosal nerve), suggested by the lacrimation and venous congestion, has proved ineffective even in expert hands. On the other hand, ergotamine, taken in time and in such a way that it is absorbed rapidly, often proves effective. Symonds [10] outlined a prophylactic regimen in which ergotamine was taken nightly during the period at risk; and Duvosin et al.[11] have emphasised that this treatment must be tailor-made for each case. They have found that inhalation of an aerosol suspension of ergotamine is effective and acts rapidly. They suggest—as did Symonds—that the risk of ergot intoxication has been exaggerated. Certainly, where the drug is needed only at the time of the cluster, liberal dosage is justified.

## DIAGNOSIS OF ŒSOPHAGEAL VARICES

THE value of radiology and endoscopy in the discovery of œsophageal varices has been compared by Conn et al.[12] in 67 cases (52 of hepatic cirrhosis and 15 of miscellaneous diseases) where both investigations were carried out. The two examinations were made within a few hours of each other, and the findings were compared on the lines of a blind trial. The radiographs were reviewed by three radiologists in turn and were re-examined by them in a random fashion, and also an immediate diagnosis was made on the wet films. Endoscopy revealed varices in 28 cases, and in 19 of these the radiological findings were positive. (The radiological concurrence was based on four out of a possible seven reports being in agreement.) It seemed from the study that radiological interpretation varied by nearly 15% in the same cases, and the individual radiologist's interpretation varied by as much as 19% in his review of the same cases. An unstated number of false negatives were encountered endoscopically during the trial; these were radiologically positive and were shown to be positive also at a subsequent endoscopic examination. Conn et al. conclude that the routine barium-swallow technique is diagnostically unreliable, especial sources of inaccuracy being coincidental small hiatus hernias or peptic œsophagitis. They admit that endoscopic errors may arise from mucosal folds being interpreted as varices.

Earlier, Friedberg et al.[13] reviewed a series of 850 endoscopies on 674 cases of liver disease, including 582 cirrhosis. They found that of 184 cases in which varices were diagnosed endoscopically 107 had positive radiological findings. 32 of their patients were reported positive by the radiologist but were negative endoscopically. Friedberg et al. found that the endoscopic findings might be subsequently negative in nearly 10% of cases where examination by this method had previously been positive. Necropsy in 29 other cases which had been positive endoscopically revealed varices in 23, and of 13 in which both endoscopy and radiology had been negative necropsy revealed varices in 6.

1. Gorham, L. W. *Arch. intern. Med.* 1961, **108**, 8, 189, 418.
2. Barritt, D. W., Jordan S. C. *Lancet*, 1960, i, 1309.
3. Hampson, J., Milne, A. C., Small, W. P. *Lancet* 1961, ii, 402.
4. Allison, P. R., Dunhill, M. S., Marshall, R. *Thorax*, 1960, **15**, 273.
5. Cooley, A. D., Beall, A. C., Alexander, J. K. *J. Amer. med. Ass.* 1961, **177**, 283.
6. Robin, E. D., Julian, D. G., Travis, D. M., Crump, C. H. *New Engl. J. Med.* 1959, **260**, 586.
7. Kunkle, E. C., Pfisffer, J. B., Wilhoit, W. M. *Trans. Amer. neurol. Ass.* 1952, **77**, 240.
8. Harris, W. Neuritis and Neuralgia. London, 1926.
9. Horton, B. T. *Proc. Mayo Clin.* 1939, **14**, 257.
10. Symonds, C. P. *Brain*, 1956, **79**, 217.
11. Duvoisin, R. C., Parker, G. W., Kenoyer, W. L. *Arch. intern. Med.* 1961, **108**, 711.
12. Conn, H. O., Mitchell, J. R., Brodoff, M. G. *New Engl. J. Med.* 1961, **265**, 160.
13. Friedberg, S. A., Bennett, H. D., Singh, H., Lindberg, J. *Ann. Otol., &c., St. Louis*, 1955, **64**, 599.

Atkinson et al.[14] reported that barium-swallow examinations in 23 patients with œsophageal varices demonstrated by portal venography was positive in 14. In 15 out of 18 patients from the series, œsophagoscopy was positive. In no case did portal venography fail to show varices demonstrated by the other two methods. Evans'[15] review of 100 patients with cirrhosis was specifically directed to assessing the reliability of a barium swallow or meal in the diagnosis of œsophageal and gastric varices. Comparing his results with that of portal venography in 48 patients, he found that an exhaustive barium technique revealed œsophageal varices in 38; venography was positive in 7 patients in whom the barium-swallow technique did not disclose varices; and in 4 patients large œsophageal varices were shown by barium examination when portal venography had failed to disclose them.

Kirsch et al.[16] compared their experience with endoscopy and radiology in 502 patients of whom 419 were cirrhotics. They concluded that of 102 patients endoscopically positive a positive radiological diagnosis could have been made in 74.

Apparently with an exacting technique radiology can provide a great deal more than an average of 20% positive finding compared with those of endoscopy.[17] Perhaps in a large series of patients good endoscopy may show slightly more positive findings than a good barium-meal technique; but neither method is infallible, both may reveal varices undetected by the other method, and even examination by the same method repeated after an interval may show different findings.

## UNDULANT FEVER

As a serious risk to human health, bovine tuberculosis is now extinct in Great Britain. Every herd of cattle is now attested and, two years after attestation is complete, the proportion of animals which react to the tuberculin test is of the order of 0·2% or less. To find a single cow excreting tubercle bacilli would probably involve examining the milk of a quarter of a million or more, and the public-health laboratories can occupy their time more profitably. After attestation reacting animals appear sporadically—probably because the tuberculin test in cattle as in man does not give its answers in black and white—but the compensation given by the Ministry of Agriculture is on a scale which does not encourage the working farmer to keep them. (We hope that all these animals are examined for active disease.) To those who remember the orthopædic wards of thirty years ago this is a victory as striking as that won over diphtheria, and it would be ungenerous to deny that the credit belongs entirely to our veterinary colleagues—and the Treasury.

What is the next move? Many doctors would agree with Dr. S. W. Savage, the medical officer of health for Warwickshire, whose father did so much to stir the public conscience about bovine tuberculosis, that an attempt should be made to end the dangers of undulant fever.[18] We can be assured that in this too we will have the support of the veterinary surgeons, if only because contagious abortion is still an unmended hole in the farmer's pocket. Milkborne infections could be abolished tomorrow if all milk were pasteurised. More than 90% of it is; but it is asking a lot to demand that every pint produced in the depths of the country be collected, pasteurised, and returned before a drop may be drunk by the producer and his family—and all this to try to prevent a relatively rare disease which causes little public alarm.

Considering that about 15% of all herds are infected with *Brucella abortus* the rarity of undulant fever in man is surprising.[19] We can only guess at approximate figures; but, of the half million people who drink raw milk, probably 500 or less develop undulant fever each year. It is not difficult to find communities which have drunk infected milk for years without a single case of infection becoming apparent. One obvious reason is that infection is not easily acquired by mouth. Garrod showed that gastric acidity gives considerable protection, and a thermometer will prove that the milk in a cup of tea is usually brought to a bactericidal temperature whether tea or milk is added first.[20] When a veterinary surgeon wishes to induce experimental infection in a calf he does not give the organisms by mouth but instils them into the eye. Universal pasteurisation would in fact be unlikely to reduce the incidence of infection by as much as half. Urban infections are now uncommon, and in a dairying district a large proportion of the patients are veterinary surgeons, farmers, their wives, and their employees. Many of these drink their milk raw; but undulant fever is a good deal commoner among the adults who handle the cows than among their children who drink more of the milk. The products of conception of an infected cow, if she goes to term, are a more or less pure culture of *Br. abortus*, and midwifery in the byre is no cleaner or more orderly than it is in the cottage. The eyes, and the cuts on the hands, of the attendants are wide open to infection. (Has anyone compared the titres of brucella antibodies in veterinary surgeons with and without spectacles?) In the U.S.A. brucellosis (often due to *Br. suis*) is an occupational disease of slaughtermen; but this risk has not had much attention here.

In many instances no dogmatic distinction can be made between milkborne and occupational infections. The relative incidence of the former would be lower if it were not for the small epidemics which sometimes occur in communities supplied from a single herd. These might be explained either by one or more cows excreting the organisms in unusually large numbers or by a strain of *Br. abortus* of exceptional virulence; but there is no firm evidence to support either hypothesis.

If man is to be freed from the danger of undulant fever no measures will suffice short of eradicating brucella infection in cattle. (Other domestic animals are susceptible to infection, but their importance to public health in Great Britain is almost certainly negligible.) This can be done. Under conditions not very different from ours the Danes have reduced the prevalence in their herds from 25% to 0·2% since 1945. The detection and slaughter of all infected animals is the only method of eradication likely to succeed. Because there is no single diagnostic method equivalent to the tuberculin test, detection will not be easy, and the compensation paid for slaughter will be expensive; but there is pretty general agreement that

14. Atkinson, M., Barnett, E., Sherlock, S., Steiner, R. E. *Quart. J. Med.* 1955, **26**, 77.
15. Evans, K. T. *Brit. J. Radiol.* 1959, **32**, 233.
16. Kirsch, I. E., Blackwell, C. C., Bennett, H. D. *Amer. J. Roentgenol.* 1955, **74**, 477.
17. Brick, I. B., Palmer, E. D. *Gastroenterology*, 1953, **25**, 378.
18. Warwickshire County Council: annual report of the medical officer of health, 1960.
19. *Mon. Bull. Minist. Hlth Lab. Serv.* 1961, **20**, 33.
20. Garrod, L. P. *J. Path. Bact.* 1937, **45**, 473.

eradication must come soon. Not as an alternative but as perhaps a preliminary to eradication the Ministry of Agriculture has announced a revised scheme for vaccination against brucellosis, to begin in 1962.[21] Calves inoculated with a living strain of *Br. abortus* of low virulence (e.g., S.19) are protected throughout their reproductive lives against any but an overwhelming infection. This vaccine has been available for at least ten years, and where it has been used conscientiously it has dramatically reduced the losses of calves. Unfortunately less than half the farmers in the country have used it, and then often in a haphazard way. Under the new scheme the vaccine will be available for calves only, without cost but without compulsion. (It is important to limit its use to calves because, given to older animals, it is likely to leave a residuum of circulating antibodies which will hinder diagnosis in any future scheme of eradication.) The arguments for and against compulsion have been endless, and we can only hope that the Minister's decision on this point is rewarded by success. There can be no doubt that wider use of the vaccine will save a lot of calves. At the same time it can be expected to reduce the number of sources of infection—and there is reason to think that only those cows which excrete the organisms in large numbers are important in the spread of infection to other cattle, and perhaps to man. On the analogy of other diseases there is no more potent way of reducing infection than by diminishing the sources of infection, and if this scheme is accepted by the farming community it may lower the incidence of brucellosis to the point where eradication will be within our means. Meanwhile the use of S.19 vaccine has introduced another occupational danger. Many veterinary surgeons have managed to vaccinate their own left hands; and the results are, to put it mildly, irritating.

## INDUCTION OF OVULATION

CLINICIANS interested in infertility may be heartened by a promising observation made by Greenblatt et al.[22] during an attempt to evaluate the anti-fertility effect of a compound known as MRL/41. This compound, which is structurally related to the non-steroid œstrogen, chlorotrianisene (' Tace '), is known to inhibit pituitary gonadotrophin in rats.[23 24] Greenblatt et al. found that MRL/41 apparently induced ovulation in a high proportion of amenorrhœic women. This effect was judged largely by the production of a typical corpus-luteum thermogenic effect, which in some cases was sustained for longer than the usual fourteen days, by studies on vaginal cells, cervical mucin, and endometrium, and by hormone assays where feasible.

With commendable caution, these workers remark that the only absolute proof of ovulation is the recovery of ova or the occurrence of pregnancy. Such final proof was in fact obtained in 4 cases. 2 of these 4 patients became pregnant during treatment and 2 after the conclusion of treatment—in 1 case three months later, after the induction of a regular ovulatory rhythm. In 4 normally menstruating (and ovulatory) women, administration of MRL/41 produced no evidence of inhibition of ovulation, though in 2 cases there was unexplained prolongation of the thermogenic effect of the corpus luteum beyond fourteen days. In 3 cases of precocious puberty, ovarian activity, judged by vaginal cells and menstrual flow, was reduced somewhat; 1 child became irritable and rebellious, and treatment had to be discontinued. In 4 cases of suspected premature menopause (the ages of the patients are not stated) and in 1 case of ovarian agenesis no effect was noted. This suggests that a potentially normal ovary is required for the compound to be effective.

Certain untoward, though not dangerous, side-effects were noted, including possible allergic manifestations and in 3 cases ovarian cysts which regressed slowly. The production of hot flushes in several patients, together with the regression of precocious vaginal mucosal development in the children, suggests that the compound is anti-œstrogenic, and that it probably acts directly on the pituitary-ovarian balance. But no alteration in the urinary gonadotrophin titre was noted in the 4 presumed menopausal women; nor was there any evidence, from studies of 17-ketosteroid excretion, that the drug inhibited adrenal function.

Ovulation is notoriously difficult to induce in the human. Apparent success sometimes attends cyclical substitution therapy, administration of corticosteroids and wedge resection of the ovaries in the Stein-Leventhal syndrome, and even pituitary irradiation; but on the whole the treatment of the anovulatory state, with or without amenorrhœa, has been disappointing. Several of the cases successfully treated by Greenblatt et al. had already failed to respond to one or more of these other methods. The results so far obtained with MRL/41 seem to give promise of a major advance in the treatment of ovulatory disorders.

21. *Times*, Dec. 11, 1961.
22. Greenblatt, R. B., Barfield, W. E., Jungck, E. C., Ray, A. W. *J. Amer. med. Ass.* 1961, **178**, 101.
23. Holtkamp, D. E., Davis, R. H., Rhoads, J. E. *Fed. Proc.* 1961, **20**, 419.
24. Segal, S. J., Nelson, W. O. *Anat. Rec.* 1961, **139**, 273.

## THE BEST YARDSTICK WE HAVE

ONE good thing that came out of the 1939-45 war was a systematic study of the effects of head injury at the Military Hospital for Head Injuries, Oxford. In civilian life trauma to the brain is common enough, but the opportunity of correlating various features is generally lacking. One such correlation—between the duration of post-traumatic amnesia (P.T.A.) and other data—has been worked out in detail by Russell and Smith,[1] who remark that the period of amnesia should be taken, not as the duration of complete loss of consciousness, but as the total period during which normal conscious functioning is impaired—the time taken for a patient to " recover his senses " [2] or to return to the state that Head [3] described as " vigilance ". In this period the patient may be comatose or, at the other end of the scale, slightly confused. The importance of its duration was indicated by Russell [4] many years ago. It comprises, as has since been learnt, the interval during which the patient is unable to store any memory of current events. Russell [5] suggested that this ability was associated with the function of the hippocampus and its connections—a view which accords with neurophysiological evidence and with clinical findings.[6]

Certain cells in the " Sommer sector " of the hippo-

1. Russell, W. R., Smith, A. *Arch. Neurol.* 1961, **5**, 4.
2. Jackson, J. H. Selected Writings (edited by J. Taylor). London, 1932.
3. Head, H. Aphasia and Kindred Disorders of Speech. New York, 1926.
4. Russell, W. R. *Brain*, 1932, **55**, 549.
5. Russell, W. R. Brain, Memory, and Learning. Oxford, 1959.
6. Scoville, W. B., Milner, B. *J. Neurol. Neurosurg. Psychiat.* 1957, **20**, 11.

campus were noted to be particularly vulnerable to anoxia.[7] Destruction of the hippocampus does not, however, produce loss of consciousness, and this confuses classification of severity of head injury in terms of "concussion". Nevertheless, Russell and Smith prefer "concussion", classified by degrees, to the terms "contusion" and "laceration", on the ground that organic damage may not be visible to the naked eye. They suggest that injuries giving rise to P.T.A. of up to an hour should be called slight concussion, of 1 to 24 hours moderate, of 1 to 7 days severe, and of more than 7 days very severe.

Cases of focal brain injury or serious injury to other parts of the body were excluded from their main analysis. In the remainder certain statistical trends were evident—for example, fracture of the skull was commoner in the more severe injuries. Other factors which showed a similar trend were motor disorder, anosmia, dysphasia, defect of memory or calculation, and retrograde amnesia of more than 30 minutes. What may be deduced is that all these features are associated with organic damage to the brain—a fact which has been disputed in relation to defect of memory or calculation. The trend was apparent in each of four statistical groups representing a total of 1324 cases, divided according to the method of reference to the hospital. By contrast, in all four groups anxiety, depression, dizziness without true vertigo, and denial of headache or complaint of acute headache were unaffected by the duration of the P.T.A. These symptoms, regarded by Russell and Smith as non-organic, were commonest in the group in which psychogenic features were prominent. Severity of injury was shown to be positively correlated with advancing age. For the same type and degree of head injury, older patients tended to have a longer P.T.A.; but in addition within any fixed P.T.A. interval the severity of the other effects of motor disorder, defects of speech, and intellect, and to a lesser extent fracture and anosmia, tended to be even more increased.

In the absence of definitive evidence of structural damage, Brock [8] described the P.T.A. as the best yardstick for assessing the severity of a head injury. Russell and Smith have shown that it can also be used statistically as an indication of organic, as opposed to non-organic, symptoms. The assessment of the individual case is thus rendered more acute—a fact of medicolegal as well as of clinical importance.

## OCCUPATIONAL HEALTH SERVICE FOR SEAFARERS?

SINCE the turn of the century much has been done to improve the amenities and conditions of service of the seafarer. In Britain the Instructions to Surveyors (1937) on the construction of living quarters for masters and crews in new merchant ships marked the successful culmination of a long campaign by marine hygiene experts and by bodies such as the Association of Sea and Air Port Health Authorities and the Royal Society of Health to secure better living and working conditions at sea. But some wanted also a system of organised medical care for seamen. In 1926 Fleet Surgeon W. E. Home [9] recommended that the medical care of British seamen should be controlled by the Ministry of Health, although the Shipping Federation had already established at major ports a system (which has since been developed more fully) of routine medical, including radiological, examination and treatment of seafarers of all nationalities. In 1943 Sir Alexander Macgregor,[10] formerly medical officer of health of Glasgow, would have had a service run by local port health authorities, more comprehensive than that of the Shipping Federation—one that would include hospital services with aftercare and reablement, bathing with disinfection and disinfestation facilities, ambulances, and hostels. Macgregor suggested that every ship's officer, as part of his training, should be taught something of first-aid, the hygiene of ships, and the treatment of venereal disease; in the larger ships they could be assisted by sick-bay stewards who had had more intensive and more practical training in the same subjects. Recommendations for better-organised and better-supervised amenities (clubs, hotels, hostels, relief of distress, &c.) at British ports were made by the Graham White Committee [11] in 1945.

In 1924 the Brussels Agreement had paved the way for the system providing follow-up treatment of venereal disease from port to port, free of charge to the seafarer—at that time no mean privilege at some foreign ports where exorbitant charges had been made. A service almost as complete as that recommended by MacGregor has been provided for many years all over the world for Norwegian seafarers by the Norwegian Government. Norwegians staff this service; and its head, a distinguished public-health doctor, was chairman of the W.H.O. study group which in 1956, having reviewed the operation of the Brussels Agreement, recommended that the Agreement should not be abrogated unless similar and adequate provisions were included in a broad international instrument for promoting the health of seafarers in general.

On larger ships carrying a ship's surgeon, health should be promoted by the ship's surgeon—although, like his opposite number ashore, he has tended to be preoccupied with curative medicine. Those without a ship's surgeon must rely mainly on the medical guides provided by several countries (the British model is outstandingly good), the use of which depends on (*a*) support from an adequately stocked medicine chest, and (*b*) an intelligent understanding of the guide. Ship's officers are increasingly assisted by medical advice by radio—an arrangement which works best when both ship's officer and doctor ashore can consult the same medical guide; and it has been known for dislocated shoulders to be successfully reduced at sea by ship's officers—"now put your heel in his armpit and push hard".

A new report by a joint I.L.O./W.H.O. committee [12] is reminiscent of the white-papers which preceded our own National Health Service. The committee agrees that where an outstandingly good service is already established it need not necessarily conform in detail to the standard pattern recommended by the committee. It urges that meanwhile immediate consideration be given to an international scheme designed to provide all ships with the three existing medical aids—medicine chests, medical guides, and the use of radio. The report constitutes a stimulus to further advance in the interests of seamen's health and welfare, and an encouragement to those who have laboured for this.

7. Corsellis, J. A. N. *Brain*, 1957, **80**, 193.
8. Brock, S. Injuries of the Brain and Spinal Cord. New York, 1960.
9. Home, W. E. *Proc. R. Soc. Med.* 1926, **19**, 95; *Lancet*, 1930, i, 423.
10. See *Lancet*, 1943, i, 807.
11. See *ibid.* 1945, ii, 54.
12. Joint I.L.O./W.H.O. Committee on the Hygiene of Seafarers. *Tech. Rep. Wld Hlth Org.* no. 224, 1961. Pp. 14. 1*s.* 9*d.* Obtainable from H.M. Stationery Office, P.O. box 569, London, S.E.1.

## Special Articles

# A SHEEPSKIN AS A NURSING AID

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Two years ago Charnley [1] wrote about the painful blisters which too often develop over the sacrum of the hospital patient. He suggested that these were caused by the moisture that tends to accumulate in a cotton sheet when it is sandwiched between the sacrum and the rubber mackintosh, especially if the patient is running a fever. Charnley reported that he had begun a trial of a fabric of woven nylon, impregnated with polyvinyl chloride, which was soft and comfortable to lie on and through which water vapour could pass easily. He also mentioned that the value of animal skins for this same purpose was well known to an older generation of surgeons in North America.

Since our country's fortune is closely related to the qualities of the merino sheep, we felt constrained, for national no less than for medical reasons, to see whether sheepskins could indeed prevent bedsores, the more so since Mr. Charnley had touched our pride by suggesting the use of a synthetic fibre as an alternative to the natural staple.

Later he put us in touch with Dr. J. D. Godfrey, of Buffalo, New York, who sent us the following information:

"For about twenty-five years I have utilized cured deer hides of our North American variety in the management of pressure sores and as a means of preventing the same. Simply stated, the method is to turn the hair side up and have a sheet only over the top. This provides a noncompressible layer beneath the patient allowing for a relatively free circulation of air and it seems they are most comfortable even in the warmest of weather. Time and again I have looked at the Horse Guards in Whitehall and noted that they sit on sheepskins through the warmest of our touring days. I believe the same principle holds true there."

With this encouragement, we started in August, 1960, to use sheepskins in the department of surgery at the Alfred Hospital. At first only a few skins were available, but, as the method proved itself, we added to the number and we now have 25 in circulation. This report describes our experience over ten months.

### SUITABLE SKINS

Merino and merino cross skins were found to be suitable, and the observations of surgeon, nurse, and patient suggest that they should have the following characteristics:

Soft wool and dense fleece: fibre diameters of 22 μ–28 μ, corresponding to the range 56s–64s quality, provide the required softness and density.

Springy or resilient wool which recovers quickly from the depressed state.

Fibres which do not cot or mat during use and washing. Lambskins may not be satisfactory.

The skins we use have an average size of 8 sq. ft. and are chrome-tanned so that they will withstand high temperature and washing without shrinking. (Before they are used, a sample from each skin is tested in boiling water.) The wool is clipped to 1 in. length, dyed a champagne colour, and dry-cleaned.

The skin is spread on top of the sheet, wool side up, and we try to persuade the patients to lie directly on it with no pyjamas or nightshirt intervening. One skin is usually big enough to cover the area of the shoulders, back, buttocks, and upper part of the thighs (fig. 1). The

**Fig. 1—On the bed.**

surface of the fleece transmits pressure evenly over a relatively wide area and there is less friction on the patient's skin. Since the wool fibres allow free circulation of air, absorb moisture up to 33% of their dry weight without feeling wet, and dissipate moisture readily, the three chief causes of pressure sores—pressure, friction, and moisture—are considerably reduced.

### SUITABLE PATIENTS

The skins have also been tried in two units in a large public hospital. We have used them chiefly for gravely ill patients who seemed likely to have a long stay in hospital. Their use has become almost routine for patients admitted with acute oliguric failure with a view to hæmodialysis. We have also tried them for patients with fractures of the long bones being treated by skeletal traction. They have proved most effective of all for old people, and it is in geriatric nursing that sheepskins may be most useful, especially for patients in their own homes when skilled nursing care is not always to be had. With the help of a domiciliary nursing service, we have recently started a trial to test them under these conditions and to study the problems of laundering in the family tub.

We cannot yet assess the value of the skins in the prevention of pressure sores, nor in the promotion of healing in an established decubitus ulcer. But we do know of the measure of comfort which they afford to our patients—to the scraggy old lady who has no protective layer of fat, but also, no less, to the big and heavy man. Occasionally a patient finds the skin too hot in summer, but the majority have been disinclined to give them up even when the outside temperature rose above 100°F. Once they have

1. Charnley, J. *Lancet*, 1959, ii, 914.

Fig. 2—Packing of drawsheet and mackintosh.

enjoyed the luxury of lying on a skin, patients are reluctant to forgo it.

When a skin has been under a heavy patient for a long time without interruption, the pile becomes somewhat flattened and lumpy and loses much of its resilience. But one skin was in continuous use for three months under a young man of 168 lb. and still remained comfortable. The skin avoids the distressing rucking of the drawsheet and of the rubber mackintosh when a patient is being nursed in the Fowler or propped-up position (fig. 2).

We have found it difficult to use the skins in the care of incontinent patients, and unfortunately these are often the patients most liable to develop pressure sores. But if incontinent patients were provided with a number of skins, a laundered skin could always be available.[2]

### LAUNDERING

At first the skins were washed by hand, but experience has shown that they can be effectively laundered and sterilised (certainly for vegetative microorganisms) by two washes in a conventional hospital laundry machine.

Using an anionic detergent developed by C.S.I.R.O. for the boiling of wool hospital blankets,[3] the skins are first washed at 100°F to remove gross soiling. After another wash of ten minutes at 160°F (1 lb. of Gardinol BW detergent for 50 gallons of water, provides sufficient wash liquor for 12 skins) they are given three cold rinses each of three minutes, followed by spin-drying for eight minutes, and are then dried in an Airspeed blanket-dryer at a temperature of 240°F. In the dryer the skins are pegged to a moving line travelling at 5 ft. per minute and make two complete circuits, each of fifteen minutes. The pile is quickly and easily restored by combing with a steel comb.

Some of our skins have now been laundered fourteen times, and none has yet been set aside.

For slight soiling, the wool is sponged with a soft cloth wrung out in detergent and dried by spreading it on the grass in the sun or stretching it on a frame in a drying wind. (A skin dried, in error, over a radiator indoors shrank and became tough and worthless.)

The possibility that the skins may act as reservoirs of pathogenic organisms could not be ignored, and for this reason we have hesitated to use them where there was a risk of their being soiled by exudate. Though Rubbo and his colleagues[4] have shown that wool fibres do not act as vehicles in airborne dissemination of staphylococci, trials are being carried out to incorporate a phenolic bactericide in the fleece which will be released when the fibre is moist and then prevent the growth of organisms in the wool.

Since our inquiry began we have learnt that sheepskins have been in use in the Druid General Hospital at Tuscaloosa, Alabama, for some years, and their value is increasingly recognised in North America.[2,5] Miss Woodruff had been using sheepskins since 1948.

### SUMMARY

Ten months' experience in the wards of an acute general hospital suggests that nursing patients on sheepskins adds materially to their comfort. Laundering is not difficult and the skins seem to stand up well to constant use and frequent washing.

This inquiry has been aided by a research grant from the Wool Research Committee.

We gratefully acknowledge the help we have received of Mrs. P. Roberts, university department of surgery; of the nurses of the Alfred Hospital and the Royal Melbourne Hospital; and of Mr. F. P. Morris of the central linen service, Royal Melbourne Hospital.

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## Points of View

### DOCTOR-NURSE RELATIONSHIPS IN A HOSPITAL ENVIRONMENT

CLAIRE RAYNER
S.R.N.

EFFORTS are continually being made to improve hospitals in ways that will appeal directly to the patient—e.g., by improved appointment systems, "harmonious" colour schemes, and outpatient receptionists. Yet complaints about lack of interest in the patient's emotional wellbeing are becoming increasingly common.

We should, I think, recognise more consciously that, just as a child may develop symptoms of disturbance because his parents have a poor marital adjustment, so patients may be troubled because of unsatisfactory relations between the nurses who give them direct and constant care and the doctors who provide the framework of that care.

During ten years of hospital nursing, I was able to observe some of the emotional responses nurses make to doctors, and vice versa.

### ATTACHMENT TO CONSULTANT

A Sister in charge of a ward that cares for the patients of only one physician or surgeon may develop a type of marital relationship with that consultant. The patients take the place of the children of the "marriage", becoming not only important in their own right but also important to the Sister in the way that their progress reflects the state of her relationship with the doctor. Thus, when a patient improves rapidly and the consultant compliments Sister on her care of that patient, she may feel the same warmth a wife feels when her husband compliments her on her management of their child. But if the consultant is unaware that his ward Sister is seeking personal compliments from him, and therefore fails to offer them, she may feel frustrated, possibly without realising it. She may redouble her efforts to care for the patients in a way

that will produce commendation from the consultant. If this has no effect, she may try to please him in ways that do not benefit but may cause them distress:

A surgeon had a ward Sister who needed commendation to make her feel secure. She was a gold medallist, and was accustomed to praise from all the people she worked with—she was a good nurse and knew it. When she was first appointed to the ward, her care of the patients was of the highest order, and the patients almost literally adored her.

However, when praise was not forthcoming from the surgeon, she turned her attention to efforts to please him personally. Thus, the hand basin in her office was reserved exclusively for his use, and a nurse was set to polish and clean this basin four times a day, whether it had been used or not. The towel had to be folded in a special fan pattern, and three or four clean towels would be discarded if the Sister thought they had been incorrectly folded. The ward charts had to be perfect, and nurses were often kept late on duty to copy out a chart if the original had been blemished in any way. The nurses were consequently very irritable and tense and transmitted this tension to the patients.

The hour before the surgeon's round was dreaded by all the patients, who were reprimanded sharply if they moved about and rumpled their beds. At the same time, the general supervision of nursing care, about which the Sister had once been so particular, deteriorated. She also showed no interest in the cleanliness of areas unlikely to be seen by the surgeon, such as the sluice and linen cupboard.

In the end, the Sister left abruptly, telling the Matron that she could not work with a surgeon who " couldn't even take the trouble to remember her name ".

Her successor was a married woman who was patently uninterested in the surgeon's responses to her personally. She gave a great deal of attention to the teaching of her nurses—an activity that was reflected as improved care for the patients. The surgeon developed a warm personal regard for this Sister, and was extremely angry with her when she left to have a baby.

In this example a form of sex war could be seen in action. The harder the first Sister tried to win praise from the surgeon, the more he withdrew, to the point where he forgot her name—a piece of discourtesy he had never displayed before with other nurses. He was possibly subconsciously aware that this Sister wanted a warm response and withheld it purposely. When he worked with the second Sister, her indifference to him caused him to develop an attachment that was probably stronger than he realised—hence his anger when she became pregnant. This anger, incidentally, was expressed in a refusal to speak to the Sister at all during her last month in her post. He made his rounds when he knew she would be off duty.

As a junior nurse, I noticed that senior nurses often developed strong emotional attachments to their consultants, and these attachments were often unrecognised as such by the nurses or the doctors concerned. If the doctors made the response the nurses wanted, the ward was usually a happy one, with junior nurses and patients happy and relaxed. If the response was lacking, the Sisters were very likely to develop obsessions about cleanliness and tidiness, distressing to staff and patients.

Interestingly enough, this state of affairs was often very quickly recognised by junior nurses, who made efforts to help the Sister. For instance, they would never speak to the doctor themselves if they could possibly help it, always calling the Sister to him.

### MOTHERING

Most hospitals have at least one ward that is extremely popular with housemen and registrars. This is the ward where " you can always get a cup of coffee " and which has a good stock of biscuits and sandwich materials, often provided from the nurse's own pocket.

These nurses take a great deal of pleasure in having the doctors around at times when they are not needed to see patients. Since they rarely meet any opposition to their wish to " mother " the medical staff, they are usually very happy, as are their juniors and patients. However, strife can arise when there are two such Sisters in one hospital:

The theatre Sister and the children's ward Sister both enjoyed entertaining the medical staff. Since the theatre Sister was rather better company, the doctors gradually drifted into the habit of spending their spare time drinking the theatre coffee. The children's ward Sister became very depressed by this, and her depression spilled over into irritation with the nurses. She also became irritable with the parents of children under the care of those doctors who had rejected her mothering by choosing to drink coffee in the theatre. One parent complained to the management committee about her brusqueness when he visited his child.

When the theatre Sister left for a senior post elsewhere, the doctors returned to the children's ward for mothering, and the Sister became her old relaxed and friendly self. The complaining parent, when his child was later readmitted, wrote to the committee withdrawing his original complaint.

In this example a woman with an excess of mothering instinct was unable to release all her emotion into the care of the children, even though she was very affectionate towards them. She needed to be a mother to all the people who came into her orbit. When she was frustrated in this, she lost some of her kindness, punishing innocent outsiders (parents) for the defections of her " motherees ". Her needs were clearly recognised by one registrar, who brought her his mending, much to her pleasure and his profit.

### PROFESSIONAL RIVALRY

A difficult problem can arise with the nurse who feels herself to be a doctor manqué. She may resent her subservient position as a nurse (however senior a nurse) and this resentment usually shows itself in a prickly attitude to the doctor, an attitude which often leads to hostility from the doctor. Even a slight complaint from the doctor is taken as a personal affront. If he should ever reprimand her in the hearing of others he is likely to arouse permanent enmity.

A highly qualified outpatient Sister created considerable annoyance among some of the doctors using the department, because of the way she interfered with clinic arrangements when she saw fit. On one occasion, she noticed a patient waiting to see a general physician. Because she thought the patient to be a classical case of thyrotoxicosis, she sent her to the endocrine clinic without consulting the physicians in question. The resulting argument between the Sister, the physician, and the endocrinologist led to the patient not being seen that day by anyone, and an already tense woman left the hospital in a storm of tears, much to the anger of her own doctor and her family.

However, there were occasions when her genuinely valuable diagnostic " eye " was much appreciated by members of the medical staff. Those doctors who were willing to accept her information and advice gracefully were rewarded with impeccably run clinics. The patients of these doctors also benefited, because it was well known among the nurses that one could do as much as one liked to help any patient of Dr. X, but woe betide the nurse who made any unusual effort (like providing a meal for a long waiting patient) for the patients of Dr. Z.

### KEEPING THE DOCTOR HAPPY

I have described some nurses with difficult personalities from the medical point of view. There are, of course, doctors who make emotional demands on their ward Sisters. My own observation has been that nurses are better able to adapt themselves to these needs, and to keep their doctors happy in consequence, than are doctors in the reverse situation.

Some doctors appear to need bolstering with a sort of

wide-eyed respect from nurses. Others are deeply embarrassed by any show of awe. Some need to flirt gently with a nurse, helping themselves to feel more secure in their own maleness. Others are almost terrified by any display of femininity from a nurse. Skill at handling these needs is often at its highest in theatre Sisters. This may be because the theatre is a tense department that attracts women with a gift for soothing tensions. It may also be because the theatre Sister has no patients on to whom she can project her loving care, and therefore transfers it to the medical staff:

A theatre Sister was known among her junior nurses as "the chameleon" because of the way she could change her personality to order. With Mr. A she was kittenish and a little helpless, usually making a minor mistake when working with him. He would enjoy teasing her about the error, and would obviously bask in her admiration of his superior ability. With Mr. B, however, she was an automaton, never making any mistakes or permitting the least distraction during his lists. Should any surgeon displease her she reversed this practice, treating the ones who wanted silence with garrulity, and the ones who wanted to be supported with friendly talk to icy silence.

### IMPROVING DOCTOR-NURSE RELATIONSHIPS

Any hospital that has a department that seems to attract more than its fair share of patients' complaints would be well advised to investigate the state of relationship between the members of the staff, before investigating the tensions between the staff and the patients. The best way to do this would be through discussion groups embracing all members. However, this may not be possible, partly for administrative reasons, partly because the relations have deteriorated too much for any discussion to be possible.

In that case, discussions within the component groups may be of help. The doctors, talking alone, may discover from their colleagues how various nurses respond to *them*, and tailor their own responses accordingly.

From my own observations, I would suggest that the first attempts at improving doctor-nurse relationships should come from the doctors. This is for three reasons:

1. Doctors have a much wider training in techniques of applied psychology, and therefore, one hopes, more insight.

2. The doctor is, by tradition, in a position of power. His example percolates through a ward with greater rapidity than does that of a nurse, hampered as she is by a combination of a subservient position and constant responsibility for the minute-to-minute welfare of the patients. (This heavy load of responsibility makes her more vulnerable, and she tends to cope with this vulnerability by making strong emotional demands which must be met before she can develop insight herself.)

3. The doctor usually has a life of his own outside the hospital which fills most of his own emotional needs fairly satisfactorily. Even though more and more nurses are married, there are still large numbers of senior nurses who are forced to find both their emotional as well as their professional satisfactions in their work.

Mental-hospital staffs are well aware that friction between doctor and nurse can have an unfortunate effect on the patient, and many hold regular group discussions designed to improve communication between the members of the staff. In general hospitals the pressure of work is sometimes said to be too great for such discussions; but even if this is so, the personnel of the hospital should make an effort to assess the relationships they form with each other. Insight into these relationships might go a long way towards improving them, and ultimately to improving the emotional climate for the patients.

## In England Now

*A Running Commentary by Peripatetic Correspondents*

AT the weigh-in last night I registered 188 lb., the same as Floyd Patterson. Mind you, the weight distribution looks a bit different from his, with a much lower centre of gravity, and a rockback compensatory curvature of the lumbar spine which the champion seems to have avoided. Perhaps his muscle tone is less overstretched. The big fight at Maple Leaf Gardens came over hot speed from Toronto and popped up on our telly at just the right moment after dinner. The womenfolk had chattered their way upstairs to powder their noses and gossip in one of the bedrooms. We turned on the old gogglebox and went three and a half rounds with Tom McNeely, until the last left hook and that blistering overhand right. The womenfolk knew there was an orgy of violence downstairs: they lingered with exquisite tact around the bathroom. And it so happens that we keep our weighing-machine in the bathroom. In fact the scales make a fair bid to be the most irresistible fitting for the attention of our guests, despite the rivalry of the fully comprehensive layout. We have even known visitors make the most unconvincing excuses for slipping upstairs to weigh themselves.

It is all such a deadly secret. None of these women will ever admit to doing it, let alone divulge what the pointer said. But sound insulation is very poor in our house, and we keep the weighing machine tucked under the wash-basin. It has to be pulled clear for anyone to stand on its little platform: the job cannot be done without one loud metallic clank for the outward trip, and another one to hide the evidence. Not that we mind offering our guests any service that would cost them a penny elsewhere, but we do so wish that they would accept the truth more cheerfully. They persist in thinking that the pointer has swung irresponsibly beyond the proper mark, so most of them then jump up and down on the platform to see if the result can be coaxed back nearer their conception of ideal womanhood. All that happens is that the mountings and springs underneath get tangled up and the indicator sticks at 14 lb. Peace of mind comes flooding back: the stupid machine is obviously haywire. How nice to be able to subtract a whole stone from what the horrid thing first whispered. Our guest comes downstairs once more serene and radiant, lovelier than ever. When the last car door has slammed and the glasses are cleared away, I creep upstairs with a screwdriver and get the scales in working order again. And honestly I did not jump up and down this time to be a fair match for Floyd Patterson.

* * *

This Christmas the nurses on my ward made a charming crib and nativity scene with dolls dressed in the national costumes of the dozen or so nurses working in it. Assuredly they have brought their gifts, and not only frankincense and myrrh, from afar to the benefit of us all.

* * *

*News from school*—"There has been an acidemic going round the school this week. When it was at its hight there were only 34 people not in bed."

* * *

D'ye ken Ward 10 with its coats so white?
And the rest o' the staff, who have all taken flight?
D'ye ken that they've left us all in a plight
As we wait for their rounds in the morning?

Yes, I ken young Sam and Alan too,
Don Nolan, Ralph Whittaker, de la Rue,
But the one for me has big eyes of blue
With her golden hair like the dawning.

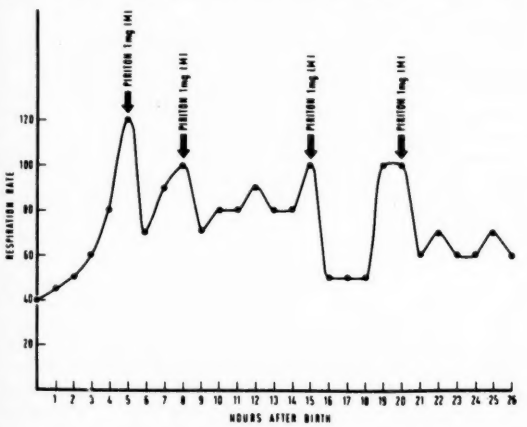
D'ye ken who I mean with face so gay?
How she worked here at Oxbridge once on a day?
Now alas she has gone far, far away
And for Blondie it's now I am mourning.

# Letters to the Editor

## ANTIHISTAMINE DRUGS IN NEONATAL RESPIRATORY-DISTRESS SYNDROME

SIR,—Kahlson's work on rats showed that there is an increased excretion of histamine in pregnancy, falling off at term, and that this is probably due to a high rate of synthesis in the fœtal liver.[1 2] Bjurö et al.[3] have shown that there is a similar although less pronounced increase in urinary excretion of histamine in pregnant women, especially those suffering from toxæmia. If the source of this histamine in the human is, as in the rat, the fœtal tissues, an infant born prematurely might suffer from an accumulation of histamine because both destruction and elimination seem to occur in the placenta. In this connection it is relevant that histamine levels in healthy newborn infants are in fact rather high.[4]

During a discussion with Dr. Michael Dawkins, it was suggested that the use of antihistamine drugs in the neonatal


PIRITON 1 mg I.M.
PIRITON 1 mg I.M.
PIRITON 1 mg I.M.
PIRITON 1 mg I.M.
RESPIRATION RATE
120
100
80
60
40
20
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
HOURS AFTER BIRTH

respiratory-distress syndrome would be worth a clinical trial. In 4 out of 5 premature babies with severe respiratory distress which seemed likely to prove fatal, 1 mg. chlorpheniramine ('Piriton') intramuscularly six-hourly seemed to lead to recovery: a 5th infant died, but his temperature was subnormal on admission and he was moribund when the treatment was started. The accompanying figure shows the effect on the respiration-rate of serial injections of chlorpheniramine in one of the babies who recovered: almost as striking was the improvement in colour and general condition and the disappearance and reappearance of subcutaneous œdema.

While the recovery of these infants may have been in spite of rather than because of the treatment, and the effect of the drug may have been due to a side-action rather than to histamine antagonism, these results seem to warrant an extended trial of antihistamine therapy in the respiratory-distress syndrome.

Institute of Child Health and
Nuffield Neonatal Research Unit,
Hammersmith Hospital,
London, W.12. J. A. DAVIS.

## EFFECT OF PARALDEHYDE ON DISPOSABLE SYRINGES AND NEEDLES

SIR,—The realisation that paraldehyde is a solvent for the plastic used in the manufacture of disposable syringes has led at least one manufacturer to include a warning notice on the card contained in each syringe envelope.

But little or no action has so far been taken to warn of the possible danger of using disposable needles for the injection of paraldehyde even if the syringe itself is made of glass. Anyone who doubts the efficacy of paraldehyde as a solvent for the plastic hub of a disposable needle should try the experiment of dropping one into a tube containing the drug: the result is the complete disappearance of the plastic hub.

Clearly, in the interval which normally elapses between the filling of the syringe and the giving of the injection, there will not be time for much plastic to go into solution. But how much can the patient safely tolerate, and what, if any, other substances commonly injected may attack the disposable syringe or needle in a similar way?

These questions require an urgent answer. Disposable needles are already in use on a large scale, and there must be many patients who have received injections of paraldehyde contaminated with dissolved plastic.

Group Laboratory, St. Peter's Hospital,
Chertsey, Surrey. ROBERT J. EVANS.

## INFECTIVE PNEUMOCONIOSIS

SIR,—Your annotation of Dec. 2 on infective pneumoconiosis in coalminers stated that tuberculosis is widely regarded as a causative factor in the disabling condition known as progressive massive fibrosis (P.M.F.). You maintain, however, that the evidence suggests a terminal rather than an ætiological role for this infection. If this view is correct, the pendulum is swinging back towards the standpoint taken in the report of the first Medical Research Council investigation in South Wales coalminers.[1 2]

The investigators were impressed by the rarity of positive findings for tubercle bacilli in the sputum of men who showed the main varieties of pneumoconiosis radiologically, in spite of the presence of tuberculous changes in a not inconsiderable proportion of pneumoconiotic lungs at necropsy—findings similar to the more recent ones quoted in your annotation. They also noted no association of tuberculin hypersensitivity or hyposensitivity with any of the main types of X-ray abnormality. They considered that "consolidation" (the approximate equivalent of the better term P.M.F.) was a stage in an orderly progression of pneumoconiosis, but that its presence possibly favoured the development of tuberculosis. The subsequent work of the M.R.C.'s pneumoconiosis research unit led to a somewhat different view—namely, that tuberculosis might be a factor in the actual development of P.M.F., and it is this view that you seem to be questioning.

It should be borne in mind, however, that pathologists have always maintained the view that the typical changes seen at necropsy in the lungs of P.M.F. cases were more suggestive of a "burnt-out" tuberculous infection than of an active one, and that experimental infective pneumoconiosis has been produced with killed bacilli as well as live ones.[3 4] Moreover, with cultures of two strains of human tubercle bacilli, the lesions of experimental P.M.F. continued to develop long after any visible organism could be demonstrated,[4] and until death of the animals.

The part played by tuberculosis in P.M.F., whether associated early or late in the latter's development, is thus complex. More information on the role of other (anonymous) mycobacteria mentioned in your annotation will be awaited with interest.

M.R.C. Tuberculosis Research Unit,
London, N.W.3. P. D'ARCY HART.
Postgraduate Medical School,
London, W.12. E. J. KING.

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## DISCS, LESIONS, AND SYNDROMES

SIR,—Biochemical research into the changes accompanying lesions of musculoskeletal tissue is the most promising approach to one of the most difficult of orthopædic problems—correlating the clinical picture with an alleged pathological process. In the diagnosis of disc lesions it could be especially useful, since none of the results of present methods of investigation are statistically impregnable. The research into changes in polysaccharide metabolism in disc prolapse, undertaken by Mitchell and Hendry, will therefore be of great value. Mr. Hendry (Dec. 16) describes some of the conclusions he has drawn from evidence provided by this work, but he has not made it quite clear how he arrives at them.

They found a lowered polysaccharide content in both the nucleus pulposus and its lumbodorsal fascia in cases of disc prolapse. It might therefore be assumed that the changes occur throughout the intervertebral segment. Whether it is possible to conclude from this that the changes affect all the intervertebral tissues equally, or whether, as Mr. Hendry believes, there is enough evidence to prove that the changes affect the disc primarily and the other intervertebral tissues secondarily, is a matter of opinion—unless there is further evidence yet to be published.

The lowering of the polysaccharide content in the area of the lesion and its elevation in the blood, which are present particularly in the acute phase, might be thought to indicate some correlation with the degree of inflammation in the lesion. Unfortunately he does not refer to this, merely concluding that the disc prolapse is secondary to the biochemical changes. If he is right, and we do not know all the evidence on which he bases this assumption, there must still be some other local change which makes one disc susceptible to the acceleration of polysaccharide catabolism, and not another. There seems no reason to suppose that this other local change is not due to the effect of instability or restriction of movement of the intervertebral joint complex.

Aberdeen. DUNCAN TROUP.

## SUPPLEMENTARY ANÆSTHETISTS

SIR,—The approaching shortage of doctors provides an opportunity to re-examine the use of specially trained nurses or technicians to give routine anæsthetics. They could be brought to something like D.A. standard, and under supervision would give safe adequate anæsthetics to a wide range of cases. Doctor anæsthetists would perhaps gain in prestige, since they would be concerned more with difficult cases and with supervision of technician anæsthetists, and I suggest that this sensible arrangement has much to commend it.

Burnham-on-Crouch, Essex. JOHN TONER.

## SUBUD AND DISTURBED BEHAVIOUR

SIR,—We have recently encountered two patients, showing gross disturbance of behaviour, who expressed delusions evidently derived in part from their experience in a spiritual sect known as Subud. It was difficult to tell whether these were shared beliefs of the sect or autistic productions of the individual.

Subud is a philosophical and religious movement originating in Indonesia. It has extended widely in recent years and now has several thousand members in this country. A central feature of Subud is a group exercise called the Latihan, aimed at removing conscious control of emotions, thoughts, and behaviour, to allow their free expression and self-knowledge. In Subud, it is believed that these exercises, particularly if they are over-indulged in, may be dangerous to certain individuals. " Subud crises " are described, in which individuals display in their everyday life behaviour normally reserved for the Latihan, so that they may need care and protection. They neglect their appearance, adopt bizarre postures, speak with " strange tongues ", and experience intense subjective changes. Our two patients would come into this category.

In the early stage of mental illness patients often seek to participate in sympathetic groups, in an attempt to reduce their distress; their illness may then be misinterpreted as a by-product of their participation in such groups. However, the Latihan may possibly precipitate psychotic illness, as certain psychotherapeutic procedures resembling it do occasionally.

In order to clarify the relationship between these attacks of acute psychiatric illness and Subud, we would appreciate hearing from anyone who has encountered similar cases.

Maudsley Hospital, London, S.E.5. JOHN FRANCIS ARI KIEV.

## HOOKWORM ANÆMIA IN COLOURED IMMIGRANTS

SIR,—Dr. Glick and Dr. Stevens (Dec. 9) rightly draw attention to this condition in London and quote details of 6 patients with hookworm infestation, of whom 5 were anæmic.

We recently completed a survey of 99 healthy coloured immigrants seen at a routine medical examination and found 13 had hookworm ova in their stools; 3 of these had mixed helminthic infestation, and there were 9 others with *Trichuris trichiura* or *Ascaris lumbricoides* infestations.

During the past two years, 25 other cases of hookworm infestation have been discovered at this hospital, new cases being found with increasing frequency as we became aware of the problem.

Only 2 of the 99 routinely examined subjects were significantly anæmic (hæmoglobin less than 11·7 g. per 100 ml.), but 10 of the 25 cases presenting at this hospital were anæmic, the lowest hæmoglobin value being 2·7 g. per 100 ml.

The occurrence of dyspeptic symptoms in hookworm disease is well recognised, and 12 of the 25 patients seen here complained of vague abdominal pains. We feel that hookworm disease should be borne in mind in all coloured immigrants who are anæmic and in those complaining of vague abdominal pains.

St. Thomas's Hospital, London, S.E.1. G. A. H. MILLER J. BAMFORTH.

## PREGNANCY AND MALIGNANT MELANOMA

SIR,—The conclusion in your leading article of Sept. 9 about the effect of pregnancy on survival of patients with malignant melanoma was based on two published studies. I tried to demonstrate (Oct. 7) how bias had been introduced into the results of these studies. Dr. White (Nov. 18) does not accept my conclusions.

A hypothetical experimental situation may illustrate my points. Suppose one wanted to study the effect of pregnancy on survival of animals with malignant melanoma. This could be done by randomising animals with the disease into two groups, one allocated to become pregnant and the other to serve as controls. If the pregnancies arose at various intervals after the onset of disease, some of the animals in the group allocated to become pregnant might die before the start of pregnancy. In evaluating the results the survival-rates after the onset of disease in the controls would have to be compared with the survival-rates in the total group allocated to become pregnant irrespective of whether they started a pregnancy or not. If the animals which died before pregnancy had been transferred to the control group in the calculation of survival-rates, the results would obviously be seriously misleading.

In the two studies in humans the rates of survival after diagnosis have been compared in females with the disease who became pregnant and females who did not become pregnant. In this way the bias mentioned above is introduced.

The second source of bias mentioned in my letter was the possible selection of females with less serious disease in the pregnant group. I agree with Dr. White that this is impossible to control. The danger in drawing firm conclusions from such material should therefore be evident.

Thus, I hold to my statement that the published material does not allow the conclusion that females with malignant melanoma may become pregnant without an adverse effect on their prognosis.

Cancer Registry of Norway,
Norwegian Radium Hospital,
Oslo.

KNUT MAGNUS.

## MANAGEMENT OF CUSHING'S SYNDROME

SIR,—It may well be that your leader of Dec. 16 summarises common opinion by writing of Cushing's syndrome that "total bilateral adrenalectomy offers the best prospect of cure". But should one use the word "cure" for so drastic a treatment after which the patient's life depends on his never forgetting or losing his cortisone pills? We also feel that your dismissal of pituitary implants with gold-198 was a little cavalier—and not quite accurate. If we set aside from our report one case due to an invasive pituitary tumour as atypical, three of the five reported cases "had striking if not complete remissions", one being a "clearly full remission". All three still seem to be complete remissions, and have no dependence on cortisone pills. Adequate assessment of this method can only follow its trial in a larger number of cases, but these were not merely "impressive though incomplete remissions".

R. FRASER
G. F. JOPLIN
J. W. LAWS
R. E. STEINER.

Postgraduate Medical School,
Ducane Road, London, W.12.

## NEUROTICS NOMINE

SIR,—Dr. Denham (Nov. 25) has shown how psychiatric patients and ex-patients can help each other during the period of rehabilitation. He describes his Association as supported by the management committee of the local mental hospital, and generously helped by the London County Council. Your readers may be interested to hear of the somewhat similar work that is being done by another Association, but without support from public funds. Neurotics Nomine owes its formation to the vision of a psychiatrist, Dr. J. Bierer, and a former patient, Mr. John Custance. Membership is open to anyone who shares the aims of the Association, which, briefly, are:

(1) To help patients and ex-patients to meet each other and people outside the Association.
(2) To assist the patient in taking the first step toward social readjustment.
(3) To support each other by meetings at home or by talking over the telephone in an emergency.
(4) To provide a panel available to discuss or answer questions to an audience of G.P.s or members of the social services.
(5) To help remove the stigma and fear that still surround mental illness.
(6) To help members by providing opportunities for useful work, social contacts, and self-expression.

It is felt that the existence of such an Association should give hope and encouragement, and provide a demonstration to those who are still ill that social readjustment is, in fact, possible.

Although there are three psychiatrists and an occupational therapist on the executive committee of Neurotics Nomine, the whole work of running the Association is done by patients and ex-patients. When the Association was founded (towards the end of 1957) some feared that it would become a happy hunting ground for pseudo-psychologists and arm-chair psychiatrists, but this has not been so, and the group meetings are purely social. Though the Association is not consciously therapeutic, the joint activities and social gatherings do have a therapeutic effect.

Neurotics Nomine now has twelve groups (seven in the London area and five in the provinces) and others are being formed. With two exceptions the groups meet in the homes of the members.

Membership has increased to nearly 300 during 1960, but the number of people helped is far in excess of that. Members often attend a group for some time, regain their social confidence, and then leave because they no longer need its support.

The Association arranges visits to the more isolated members and those in hospital, and publishes a quarterly magazine of high standard. The Association depends entirely on the voluntary subscriptions and donations of its members. The fact that members of psychiatric clubs have to find their own funds gives them an added pride in and appreciation of their clubs.[1]

New members are gained largely by letters in local papers and by word of mouth, but an increasing number are referred by psychiatrists and social workers. If any of your readers would like further information we shall be pleased to hear from them.

38, Marlborough Place,
London, N.W.8.

J. HOUSDEN
Honorary Secretary, Neurotics Nomine.

## HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

SIR,—In their interesting paper of Dec. 9 Dr. Ginsburg and Dr. Brown found an increased excretion of œstrogens in 10 patients in whom the joint condition complicated bronchial carcinoma.

2 of these patients had gynæcomastia, but their œstrogen levels were less than in several others with no feminising signs. From these results, and the finding of normal œstrogens in 2 patients with pulmonary tuberculosis and gynæcomastia, they suggest that feminising changes in the male may depend on factors other than œstrogen production.

This view would not accord with a case of bronchial carcinoma and gynæcomastia I have reported,[2] in which the œstrogen excretion was 3 times the normal, but there was no arthropathy, except for minimal tibial periostitis.

It is usual for joint pain and swelling to regress immediately after resection of the lung tumour, as in case 8 in Dr. Ginsburg and Dr. Brown's series. It is difficult to relate this to the urinary œstrogen levels, which, in this case, remained high for a further 3–4 weeks. It may be that the postoperative œstrogen concentrations more closely parallel the periosteal changes which, as Dr. Holling and colleagues (Dec. 9) have shown, can take several weeks to regress after operation.

Sully Hospital,
Penarth, Glamorgan.

K. P. GOLDMAN.

## GIANT-CELL ARTERITIS

SIR,—The cases described in Dr. MacGregor's interesting article (Nov. 25) seem to me to form a rather heterogeneous group. Some of them, for example, seem to be instances of Coxsackie or Echo viræmias with rather protracted sequelæ (a not too rare phenomenon). The therapeutic response to steroids cannot be taken as prima-facie evidence for a collagen disease.

I have observed several similar cases in young people in their twenties, occasionally in their late teens. Indeed, a 22-year-old girl quite like Dr. MacGregor's case 6 was referred to me. I believe (I am ashamed to admit it) that I biopsied every organ that could be biopsied—and, finally, after months of research, it turned out that a Coxsackie B infection was the probable cause of her strange illness. I also recall seeing a similar picture in two youths who had had german measles.

1. Blair, D. *in* Therapeutic Social Clubs (edited by J. Bierer). London, 1948.
2. Goldman, K. P. *Brit. J. Dis. Chest*, 1961, 55, 162.

Giant-cell arteritis is apparently a rather rare disease. So, either we do not diagnose it enough because of our strict adherence to procrustean diagnostic criteria, or many physicians simply do not know enough about the disease. Be that as it may, in the absence of histological corroboration of Dr. MacGregor's cases, one could only guess at their real nature. But this does not detract from his merit in calling attention to an interesting group of diseases. Whether "polymyalgia rheumatica" is a variant of the same disorder(s) or some distinct entity, I do not know.

Bronx, New York. MARDOQUEO I. SALOMON.

## A CASE OF PARTIAL TRISOMY

SIR,—Dr. Patau and his colleagues (July 22) suggested that many patients who display various combinations of the anomalies of the syndromes caused by trisomy 17–18 and 13–15—but have 46 chromosomes—might be instances of partial trisomy (i.e., the presence in triplicate of only part of the respective chromosome, the extra segment being attached to, or inserted into, another chromosome). The structural alteration of the recipient chromosome is assumed to be usually too small to be detected microscopically.

We describe below a probable case of such a partial trisomy in a male, the trisomic segment being attached to chromosome 21 or 22. We find in our patient only 4 small acrocentric chromosomes, 1 being readily distinguishable as the Y chromosome. Another—abnormal—chromosome is present with the centromere submedian, the long arm having the length of those of the small acrocentric chromosomes, the short arm having about the same length as the short arm of 17 or 18. We have seen this chromosome clearly in all the 40 karyotyped cells of the leucocyte culture of the patient (fig. 1). A buccal smear and a skin biopsy for sex chromatin are read as being chromatin-negative.

The patient is a 20-year-old young man, height 6 ft. 2 in. (188 cm.), arm span 6 ft. 1 in. (185 cm.). There is distinct webbing of the neck. The hair grows down to low in the neck. The ears are low set and malformed. The mandible is small (fig. 2). There is no fusion or absence of the cervical vertebræ. Physical examination of heart and lungs reveals nothing abnormal, but there is a distinct pectus excavatum. Hands and fingers show no unusual features, but the feet are malformed and small. The ankle-joint is limited in its movements. The toes overlap. As a boy the patient was operated on for an inguinal hernia. The external genitals are normal. There is a mild form of epilepsy. Mentally he is slightly subnormal. His mother, who was 29 at the boy's birth, had an uneventful pregnancy; his father was then 35. Both have always been in good health. There are two other children, older than the patient; both are mentally and physically sound.

We think that this is a case of a partial trisomy. The responsible "trisomic locus" is possibly part of chromosome 17 or 18, because the anomalies in our patient are partly those found in the trisomies of this chromosome.

University Department of Obstetrics and Gynæcology, St. Radboud Ziekenhuis, Nijmegen, Netherlands.
J. A. M. VAN WIJCK
G. A. J. TIJDINK
L. A. M. STOLTE.

## CHROMOSOMAL CONSTITUTION IN GLUCOSE-6-PHOSPHATE-DEHYDROGENASE DEFICIENCY

SIR,—de la Chapelle et al.[1] reported the case of a female child with hæmophilia whose father was normal. A similar previous report had been explained by an XY sex-chromosome constitution, but de la Chapelle's case

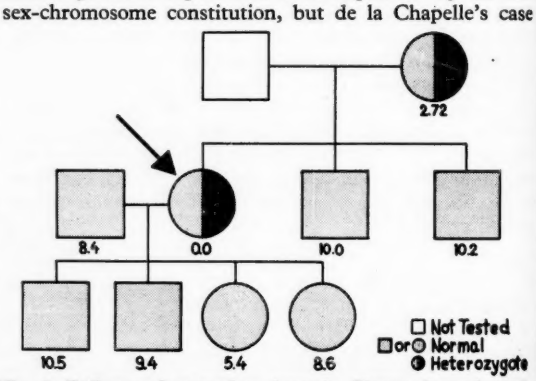


**Fig. 1—Pedigree of propositus (arrow). Figures beneath each member of kindred represent levels of glucose-6-phosphate-dehydrogenase. Older daughter of propositus has erythrocyte G.-6-P.D. level which is at lower limit of normal. She may also be a heterozygote although this cannot be established at present.**

was shown to have a normal female karyotype. We have recently made similar observations on a female heterozygote with another sex-linked defect, glucose-6-phosphate-dehydrogenase (G.-6-P.D.) deficiency.[2]

1. de la Chapelle, A., Ikkala, E., Nevanlinna, H. R. *Lancet*, Sept. 9, 1961, p. 578.
2. Beutler, E. *Blood*, 1959, **14**, 103.

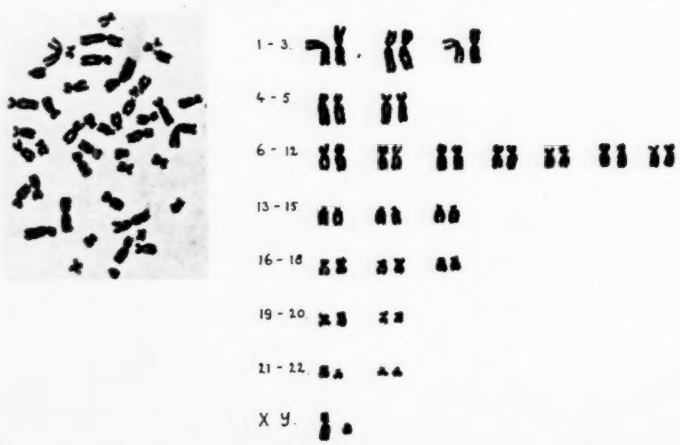


**Fig. 1.**

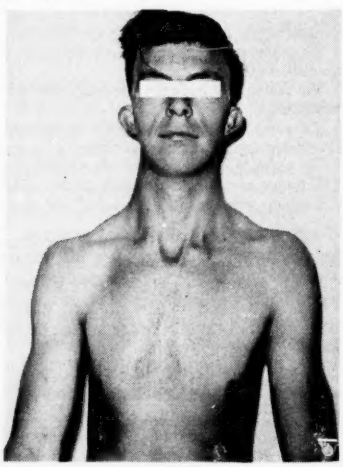

**Fig. 2.**

**Fig. 2—Chromosome karyotype of propositus, illustrating normal X chromosomes.**

The propositus is a Sephardic Jew of Syrian and Iraqui ancestry. For many years she had had severe hæmolytic anæmia each spring after the ingestion of fava beans. Since the cause of her hæmolytic anæmia was ascertained three years ago she has abstained from fava beans and has had no further hæmolysis. It is clear from the pedigree in fig. 1 that this patient cannot be homozygous for G.-6-P.D. deficiency, inasmuch as she has two normal sons. It is perhaps not generally realised that females heterozygous for this condition often do not have intermediate levels of G.-6-P.D. A pedigree similar to ours has been reported by Gross et al.,[3] and examination of pedigrees presented by others makes it very clear that penetrance of this defect in heterozygous females is exceedingly variable. Assay of G.-6-P.D. in the red cells of our propositus by a modification of the method of Kornberg and Horecker has repeatedly revealed no detectable enzyme activity (normal $=9{\cdot}1 \pm 4{\cdot}0$, average $\pm$ 2 standard deviations).

Buccal mucosal cells have been studied, and single sex-chromatin bodies identified in approximately 50% of the cells. The karyotype of this patient was determined from peripheral-blood leucocytes by the culture method of Moorehead et al.[4] (fig. 2). It is of interest that this patient's karyotype is normal. The very high penetrance of her abnormal gene is not to be explained through an XO or XY sex-chromosome constitution. Further, these studies demonstrate that no morphological abnormality of the X chromosome is associated with this genetic defect in Caucasians.

These studies were supported, in part, by U.S.P.H.S. grants H5292, and C5138. We gratefully acknowledge the permission of Dr. Joseph Golenternick to study this patient.

J. TRUJILLO
V. FAIRBANKS
S. OHNO
E. BEUTLER.

City of Hope Medical Center,
Duarte, California.

## MENTAL DEFICIENCY AND KLINEFELTER'S SYNDROME

SIR,—It has been assumed that some degree of mental deficiency is to be anticipated in patients with chromatin-positive Klinefelter's syndrome. Sohval [5] suggests that "mental function is apt to be seriously impaired" while others contend that mental deficiency is "likely" [6] or "often associated" [7] with the syndrome. The impression from these statements is that most patients with Klinefelter's syndrome have some degree of mental deficiency.

The assumption that the two conditions frequently coexist has probably arisen from the common practice of uncovering cases of Klinefelter's syndrome from among mental defectives in institutions. However, in a series of patients with Klinefelter's syndrome selected from infertile males,[8] only about 25% had "subnormal intelligence". In a series collected from a population composed of young men with I.Q.s above 70,[9] now expanded to 39 cases, the I.Q. range was 80 to 116, with an average of 96, closely approximating that of the population sampled. The incidence of Klinefelter's syndrome in this population was 0·15%.

On the other hand, Gustavson and Akesson [10] have suggested that such sex-chromatin aberrations are more often associated with a mild degree of mental retardation (I.Q. 70–85) than with more severe mental deficiency. The presumption is based on the absence of sex-chromatin abnormalities in 48 males with severe mental deficiency. The failure to find abnormalities in this small sample reflects only the inadequate size of the sample studied. Only one survey has found the incidence of chromatin-positive Klinefelter's syndrome in mental defectives to be as high as 1 in 48.[7]

The more reasonable view is that chromatin-positive Klinefelter's syndrome is at least three to six times more frequent among mental defectives than among males with average intelligence. But since mental deficiency (I.Q. below 70) is found in only about 1 of every 70 males,[11] the syndrome will be found much more frequently in those with normal mental development.

Southwestern Medical School,
University of Texas,
Dallas, Texas.

NORMAN M. KAPLAN.

## DIFFERENTIAL TRANSMISSION OF DOWN'S SYNDROME (MONGOLISM)

SIR,—The important paper by Mr. Hamerton and his colleagues (Oct. 28) raises the interesting question why the translocations they describe are exceedingly rare in the population, and not very common. They draw the interesting analogy with the *t* locus in mice where some genes (or more probably complex chromosomal rearrangements) are common in wild and laboratory stocks, despite the fact that they cause lethality or sterility in the homozygous condition. The high frequence of these genes stems from the fact that mendelian ratios are disturbed, there being a big excess of heterozygotes among the progeny from male heterozygotes.

Now Hamerton et al. report a disturbed segregation among the offspring of translocation carriers. An examination of their data suggests that the segregation ratios depart so radically from mendelian expectation that, from this point of view, the translocation must be at a very great selective advantage, despite the production of mongols among the progeny of female carriers. In fact the advantage must be as great as that shown by several allelomorphs at the *t* locus in mice.

If this "abnormal" segregation of the translocations is real, as the $\chi^2$ values suggest, and not due to chance, then there must be some additional severe disadvantage in being a carrier to account for the rarity of the condition in the population, a disadvantage which is not apparent at once from the pedigrees. The most likely explanation is that the carriers are on average far less fertile or have a much poorer expectation of life than "normal" people.

Hamerton et al. point out that there are eight possible types of gametes that might be produced by a translocation carrier, and furthermore that three of these designated by them—Ia, Ib, and IIa—are known. The presence of a fourth—IIb—is inferred from family studies. The production of gametes IIIa and IVa has not yet been demonstrated, and might be expected to be less common under normal circumstances. However, if there is a tendency for such gametes, which possess the translocation, to be formed, and if the resulting trisomic zygotes are lethal, the necessary disadvantage of the translocation would be explained. But this disadvantage would result only if the

3. Gross, R. T., Hurwitz, R. E., Marks, P. A. *J. clin. Invest.* 1958, **37**, 1176.
4. Moorehead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., Hungerford, D. A. *Exp. cell Res.* 1960, **20**, 613.
5. Sohval, A. R. *Amer. J. Med.* 1961, **31**, 397.
6. Mosier, H. D., Scott, L. W., Cotter, L. H. *Pediatrics*, 1960, **25**, 291.
7. Prader, A., Schneider, J., Frances, J. M., Züblin, W. *Lancet*, 1958, i, 968.
8. Ferguson-Smith, M. A., Lennox, B., Mack, W. S., Stewart, J. S. S. *ibid.* 1957, ii, 167.
9. Kaplan, N. M., Norfleet, R. G. *Ann. intern. Med.* 1961, **54**, 461.
10. Gustavson, K. H., Åkesson, H. D. *Lancet*, Sept. 23, 1961, p. 724.
11. Burt, C. The Subnormal Mind. Oxford, 1955.

consequent partial infertility is not compensated for by additional pregnancies to replace lost foetuses.

It is suggested therefore that the abnormal segregation, whether it be due to preferential gamete formation or subsequent preferential fertilisation, may apply to all gametes carrying the translocation including IIIa and IVa which have not been detected because they cause early loss of the embryo. Since the postulated loss must be large to compensate for the observed segregational advantage of the translocation, it should not be difficult to detect it when more families are available for study.

Subdepartment of Genetics,
Liverpool University. P. M. SHEPPARD.

## CARCINOGENS IN PATHOLOGICAL LABORATORIES

SIR,—In my recent visits to pathological laboratories I have been amazed at the free-and-easy use of benzidine—a substance handled with great care in industry and manufactured only in special modern plants. I would refer pathologists to a recent article.[1] Are there any statistics regarding bladder tumours in pathological-laboratory workers?

Spondon, Derby. O. P. LLEWELLYN.

## ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION

SIR,—Dr. Poller (Oct. 28) has repeated his objections to our paper of Aug. 12, but has not been able to produce any new evidence.

We have demonstrated (Oct. 7) that our two large groups of patients were statistically excellent counterparts and met the requirements mentioned by Dr. Poller (Aug. 19). Dr. Poller now says that he is still not satisfied, without giving any specific cause.

Concerning the effect of subcutaneous heparin, he is inclined to agree that the action of the heparin we gave may have been sustained, but he claims that we did not show it was effective in our cases. Probably Dr. Poller overlooked the reference to a recent study by one of us in which the effect of such treatment was demonstrated. As we used the same preparation in the same doses there is no reason to doubt its efficacy.

Regarding laboratory control of dicoumarol treatment with the Quick or the P & P method, Dr. Poller definitely states that the Quick method gives a greater reduction of coagulability than the P & P method. This statement certainly gets no support from a recent very careful study,[2] showing virtually no difference between the amount of dicoumarol given to maintain patients in the therapeutic range as measured by either the Quick or the P & P method.

The main point, however, is that in the treated group we demonstrated a pronounced reduction in thromboembolic episodes but without a reduced mortality.

If a trial of anticoagulants shows no benefit, Dr. Poller says it is necessary to look for a cause. In our trial the cause, he believes, is that the drugs were given unwisely and ineffectively. This argument is not without psychological interest. It may be, however, that the cause is very simple—that anticoagulants are of no benefit in the treatment of acute myocardial infarction.

Dr. Williams (Nov. 18) asks whether we took our own advice and discontinued anticoagulant therapy in patients with acute myocardial infarction. Yes, of course we did. Anticoagulants are not given in the four medical departments headed by us.

Before we published our work, anticoagulants were given to patients with acute myocardial infarction in all the medical departments in Greater Copenhagen. Today this treatment is not given at all in 13 medical departments, only to selected cases in 2 departments, and to all patients with acute myocardial infarction in only 6 of the 21 medical departments in this area.

Kommunehospitalet,
Medical Departments 2 and 3, and
Bispebjerg Hospital,
Medical Departments B and C,
Copenhagen,
Denmark.

TAGE HILDEN
KURT IVERSEN
FLEMMING RAASCHOU
MICHAEL SCHWARTZ.

1. *Brit. J. Urol.* 1961, **33**, 86.
2. Rodmann, T., Pastor, B. H., Fawcett, K. C. *Amer. J. Med.* 1961, **31**, 547.

## AUTOTRANSFUSION

SIR,—It is becoming increasingly common for anæsthetists to ask for a bottle of blood to be provided as a "standby" for surgery, even when the patient is not anæmic. May I suggest that some of the patient's own blood should be withdrawn one week before operation for use during the operation? This would have the following advantages:

1. Assured compatibility—no matching needed.
2. The patient would already be in the phase of blood regeneration by the time the operation was begun and he would have a flying start on any hæmorrhage.
3. Assuming that the loss of his original pint of blood reduced his hæmoglobin level from 100% to 90% of normal, a further hæmorrhage of 1 pint would mean a net loss of only 9/10ths of the volume of red cells which would have been lost had his hæmoglobin been 100%.

On this last basis one could develop an argument for exsanguinating the patient at the commencement of surgery with subsequent replacement.

Pathology Department,
Whipps Cross Hospital,
London, E.11. W. W. WALTHER.

## CAUSE AND EFFECT IN PERIPHERAL NEUROPATHY

SIR,—I read with interest Dr. Steer's letter of Nov. 11 on the relation of diseases of the gallbladder to brachial neuropathy.

An average-sized woman of 54 was first seen in 1959, with seven years' history of indigestion, epigastric pain, eructations while lying down, and occasional attacks of heartburn. Eighteen months earlier she had had a hæmatemesis. Barium meal showed a large hiatus hernia, which was repaired through a thoracotomy incision. A few gallstones were palpable in the gallbladder.

Three months after her operation, she had a sudden attack of epigastric pain, radiating to her neck and right ear and down to her right elbow. Barium meal, this time, was negative; there was no peptic ulceration or recurrence of her hiatus hernia. Medical treatment did not help her. The epigastric pain persisted, and the arm pain worsened. This she described as "rheumatism pain", radiating from her scapular region, along the outer aspect of the limb to the hand. Occasionally, she had "pins and needles" and shoulder pain on attempting to lift the right arm. There was tenderness on attempting to brace her right shoulder passively, and slight wasting and weakness of the right thenar muscles.

She underwent cholecystectomy and routine appendicectomy. Many small pigmented stones were found in the gallbladder, which showed subserosal fibrosis and traumatic ulceration of the mucosa. She made an excellent recovery. Two days later the pain in her right hand had disappeared. She left hospital relieved of all pain, and able to put her right shoulder comfortably through its full range of movement.

This case supports the view that gallbladder disease can cause brachial neuropathy. The similarities in pain distribution and the dramatic effects of cholecystectomy in these two cases suggest that there is a "cause and effect" relation between diseases of the gallbladder and a form of brachial neuropathy.

Referring to the article of Dr. Lishman and Dr. Ritchie Russell (Oct. 28), it now seems that some affections of

the gallbladder have a place, however humble, among the many causes of brachial neuropathy.

I am very grateful to Mr. A. K. Price, who has kindly encouraged me to write this letter.

St. Martin's Hospital,
Bath, Somerset. ADELOLA ADELOYE.

## INSULIN THERAPY

SIR,—While aware of the risk of being regarded as an old-fashioned psychiatrist, I am rather concerned about the fact that I have in the past year seen two cases of florid paranoid schizophrenia which failed to respond to the usual doses of the newer drugs.

One of these patients was from West Germany and it was fortunately possible for her to return to her native town where her own doctor arranged for her to have a course of deep insulin therapy. The second patient had had a full course of deep insulin some years previously and this apparently produced a satisfactory remission. She is still ill, and it is now impossible to give her a repeat course because of the crucial shortage of nursing staff.

I wonder whether any other psychiatrist has had a similar experience and whether deep insulin therapy is now carried on at any hospital in the National Health Service. It may be that one centre would suffice for such an elaborate treatment if the need is great enough.

Menston Hospital,
Ilkley, Yorkshire. A. D. COLLINS.

## IATROGENIC DISEASES OF THE NEWBORN

SIR,—I share the view (expressed in your leader of Sept. 30) about the vitamin-K analogue, 'Synkavit'. I have had the same clinical and experimental results; and I believe that toxic changes due to vitamin-K analogues depend on the dose.[1 2] In spite of these results we read again and again that vitamin-K analogues are always toxic. Your leading article puts the situation in the right light.

University Clinic of Pædiatrics,
Würzburg, West Germany. J. STRÖDER.

## "IATROGENIC"

SIR,—In the September issue of *Hellēnikē Iatrikē*, a reviewer draws the attention of doctors to the danger of incautiously used hypotensive drugs, which can lead to *iatrogenous* cerebral incidents. The word is ἰατρογενοῦς (genitive case) and is in quotation marks.

London, N.W.1. DAPHNE GLOAG.

## CONVALESCENCE AFTER APPENDICECTOMY AND HERNIORRAPHY

SIR,—Many patients who are discharged from hospital after uncomplicated appendicectomies and herniorraphies seem to need extended convalescence before becoming fit for work. In one of our major public schools boys are fit for fives two weeks and for rugby three weeks after appendicectomy. Convalescence is necessary and will vary in time as people vary in nature, but in our experience the time allowed off work often seems very long.

We should like to ask your readers what periods of convalescence they think advisable in (*a*) uncomplicated appendicectomy and (*b*) simple inguinal herniorraphy in fit men, thirty years old. In each case how long should it be before return to: (1) office-type sedentary work; (2) light manual work (no unduly heavy lifting); and (3) heavy manual work (unrestricted labouring)?

Fawley, Hants. A. WARD GARDNER.
Dibden Purlieu, Hants. G. MATTHEWS.

1. Ströder, J., Künzer, W., Mülke, G. *Klin. Wschr.* 1957, **35**, 857.
2. Ströder, J., Künzer, W., Mülke, G. *Disch. med. Wschr.* 1959, **84**, 1553.

## HALOTHANE

SIR,—I read with interest Dr. Woods and Dr. Brown's reference (Dec. 9) to halothane and adrenaline, and I should like to endorse their statement that the danger lies in intravascular injection.

In the E.N.T. department of this hospital, Mr. H. Anderson and myself have used 2 ml. of 1/15000 adrenaline in approximately 200 intra-aural operations. During this injection, a careful check was kept on the pulse in one arm, and a pulsemeter was used on the thumb of the other arm. We observed nothing significant, but on three occasions there was slight tachycardia—an increase of 10 beats. In my opinion this was due to the stimulus of the needle on the meatal skin under too-light anæsthesia.

I have questioned at least ten anæsthetists about halothane and adrenaline and all use it, despite lip service to the contrary.

Little Bromwich General Hospital,
Birmingham. EUGENE THOMAS.

## HYPOTENSION ASSOCIATED WITH PHÆOCHROMOCYTOMA

SIR,—The reports in your issue of Oct. 21 of death from phæochromocytoma, and hypotension due to this tumour, bring to mind a young man who died in this hospital after an illness of twenty-four hours, and at postmortem was found to have large bilateral phæochromocytomas.

A man aged 35 was admitted because of hæmatemesis. He became ill on the day before admission and complained of penile pain and dysuria. From the onset of the illness he had passed small amounts of urine every fifteen minutes or so, and frequently vomited small amounts of black material. His general practitioner noted a temperature of 100°F, profuse perspiration, pain in both loins, and "a rash". When first seen in hospital twenty-four hours after the onset of his illness, he complained of pain in both legs and stinging pain at the tip of the penis. He continued to vomit small amounts of altered blood. The only feature in his past history was an incident of hæmoptysis two years previously which had been investigated at another hospital with negative results.

His temperature was 101°F. He was extremely restless, continually throwing himself about the bed. His complexion was heliotrope, and there was a confluent erythematous macular rash over the trunk, but no petechiae. This rash had been present for some months. The radial pulses could not be felt, and both hands and feet were cold. Both carotid and femoral pulses were bounding. The blood-pressure on admission was 95/0 mm. Hg but within forty-five minutes a reading could not be obtained. A further forty-five minutes later he became extremely cyanosed and died. The hæmoglobin on admission was 15·3 g. per 100 ml.

The main features of postmortem examination were: no abnormality of stomach or intestine, marked hypertrophy of the left ventricle, and a recent cerebral hæmorrhage of 0·5 cm. in diameter in the putamen of the right lentiform nucleus. The kidneys were normal but both suprarenal glands were extremely large, the left weighing 750 g. and the right 430 g. They both consisted of white tumour tissue with areas of necrosis and hæmorrhage. There was a blood-filled cyst 5 cm. in diameter in the left gland. Adrenaline and noradrenaline assays were not made. No evidence of secondary deposits was found.

This case interested us because of the shortness of the illness and the absence of previous symptoms. Significant hypertension seems to have been present for an indefinite time, as shown by hæmoptysis, left ventricular hypertrophy, and a small cerebral hæmorrhage. But the patient was hypotensive terminally, possibly because of an adrenaline effect. On the other hand, the hypotension may have been caused, at least partly, by adrenal apoplexy, in view of the hæmorrhage into both glands.

Features present in this case, but not in recently reported ones, were the severe penile pain and dysuria, and the pain down both legs. Despite the large size of both tumours, no

abnormal masses were felt by a surgeon, two house-physicians, and a medical registrar. Phæochromocytoma is a rare tumour, and bilateral ones even more so (9% of all cases of such tumours [1]). Bilateral tumours have been found to occur more commonly in cases with familial incidence.[2]

It is surprising that the patient and his relatives gave no history of previous illness attributed to these tumours.

Stobhill General Hospital, Glasgow. ROBERT D. KENNEDY.

## COLLES' FRACTURE

SIR,—Your suggestion (Oct. 28) that internal fixation with a Steinmann's pin may be considered in certain types of Colles' fracture is astonishing.

The reason why deformity often recurs after accurate reduction is because the conventional forearm plaster cast provides very insecure fixation. Lambrinudi pointed out years ago that supination of the distal fragment (radial deviation is an optical illusion) is an important deformity; that pronation was an essential manœuvre during reduction; and that the position after reduction was only stable when the forearm was locked in pronation in a plaster cast extending above the elbow.

This is not required in every case, especially in elderly women, but it is essential in patients, particularly working men, in whom good function will depend upon union in an anatomical position.

London, W.1. J. S. BATCHELOR.

## HYPERKALÆMIA IN CERTAIN PSYCHIATRIC DISORDERS

SIR,—At the 3rd World Congress of Psychiatry in Montreal last June, one of us (A. M. A.) showed that certain disturbances in water balance occur in psychiatric patients after different methods of electrical treatment. We have since been studying the electrolyte balance in psychiatric patients before and after such treatment.

Of 33 cases so far investigated, 21 showed definite persistent increases in serum-potassium, ranging from 6 to 8·5 mEq. per litre. Urinary excretion of potassium was also increased, while the sodium concentration in both blood and the 24-hour urine was within normal limits.

Our experience points out the importance of the potassium ion in psychiatric disorders. One of us (M. A. M. A.-F.), while studying the electrolyte balance in mentally defective subjects, found considerable disturbances, with a particular rise in serum-potassium, in some mentally defective children with normal aminoacid excretion. The rise in serum-potassium was also accompanied by increased urinary excretion. Moncrieff [3] pointed to the electrolyte disturbance (mainly hypernatræmia) as a manifestation of certain forms of mental deficiency, but he did not mention potassium changes.

A detailed account of this and further work will be published later.

Departments of Chemical Pathology and Psychiatry, Cairo University. M. A. M. ABUL-FADL A. M. ASKAR.

## A TRIAL OF YOMESAN IN HETEROPHYES HETEROPHYES INFECTIONS

SIR,—In searching previously for an effective drug in *Heterophyes heterophyes* infections,[4] we found that treatment with piperazine adipate gave a cure-rate of 55% when used in a total dose of 6·3–22·5 g. for two to ten days, with few side-effects except in those taking more than 3·6 g. daily.

More recently we have used Bayer 2353 ('Yomesan'). Chemically this is N-(2′ chloro-4′ nitrophenyl)-5-chlorosalicylamide, and it is supplied in tablets of 0·5 g.

Our 10 cases were chosen from the outpatient clinic of the Mataria Collective Unit, Dakahlia Governorate, Southern Province of the United Arab Republic. Their ages ranged from 10 to 20 years, and they weighed between 30 and 70 kg. (66 and 154 lb.). The drug was given for seven days: two tablets (1 g.) on the first day, and then one tablet daily. The patients took the drug on an empty stomach, eating their usual breakfast two hours later. The drug was well tolerated, and no side-effects were reported. The stools were examined twice weekly for two months.

Only 4 cases (40%) responded to the treatment, their stools being negative within three days of finishing the last dose of the drug.

Department of Parasitology and Endemic Diseases, Faculty of Medicine, Ein Shams University, Cairo. H. F. NAGATY H. M. KHALIL.

## AUTOIMMUNITY AND DUPUYTREN'S CONTRACTURE

SIR,—We wish to draw attention to the work of Dr. Hanno Millesi of Vienna and to his original and thoughtful thesis of the autoimmune basis of Dupuytren's contracture.[1]

He describes an alteration with age in the structure of the palmar fascia and postulates that this induces a series of autoimmune changes ending in its replacement by reparative tissue in that region which we recognise as Dupuytren's contracture. Many original observations are included in Millesi's paper in support of the altered palmar fascia. To prove this hypothesis Millesi used intradermal injections of homogenised Dupuytren's tissue removed at operation and claimed 70% positive weal reactions, a similar response in other persons with Dupuytren's contracture, and none in normal persons without Dupuytren's contracture.

It was to test this surprising reaction to autogenous skin tests that an attempt was made to reproduce exactly the experiments of Millesi.

The abnormal palmar fascia of patients with Dupuytren's contracture was excised at operation, ground for three minutes in physiological saline with a pestle and mortar, and allowed to stand for 30 minutes; the supernatant was then drawn off and injected intradermally as a skin test in the arm. Strict asepsis was maintained, the procedure being completed in the operating-theatre during the wound closure. The tissue suspensions were standardised by sample estimations of dried weight in each case and in this experiment, 0·5 ml. was injected intradermally into the patient from whom the tissue was removed, another patient with Dupuytren's contracture and 2 persons without Dupuytren's contracture, as controls. The injection site was read at four, eight, twelve, and twenty-four hours and daily to fourteen days.

There was no positive reaction in 23 patients operated on for Dupuytren's contracture and subjected to this intradermal test. There were 2 positive reactions in 69 control patients, one being in our anæsthetist acting as a control with Dupuytren's contracture but in whom no positive reaction was obtained three weeks later when tissue from the patient's other hand was used for the injection; the other reaction being in a twenty-year-old nurse without Dupuytren's contracture. We can offer no explanation for these two positive reactions.

Millesi's interesting and original theory of the ætiology of Dupuytren's contracture introduced such new concepts that it was felt necessary to repeat and confirm his clinical investigation of his hypothesis. Our failure to reproduce his results does not disprove an autoimmune basis for Dupuytren's contracture, since we consider his intradermal test itself to be at fault in using the newly formed tissue, rather than the original altered palmar fascia which he postulated.

This technique of injection of homogenised tissue back into the host has been reported from the same clinic by Winkler [2] who claims similar results with keloid suspensions to those of Millesi with Dupuytren's tissue suspensions.

1. Symington, T., Goodall, A. L. *Glasg. med. J.* 1953, **34**, 75.
2. Kelsall, A. R., Ross, E. J. *Lancet*, 1956, ii, 273.
3. Moncrieff, A. *ibid.* 1960, ii, 273.
4. Nagaty, H. F., Khalil, H. M. *ibid.* 1960, i, 978.

1. Millesi, H. *Beitr. klin. Chir.* 1959, **198**, 1.
2. Winkler, E. *Klin. Med. (Wien).* 1960, **15**, 254.

These workers in Vienna have postulated an important new hypothesis and have attempted to confirm this experimentally. Our failure to obtain the same results leads us to suggest that other investigators should repeat this work or suggest possible lines of further investigation.

Plastic Surgery Unit,
Repatriation General Hospital,
Heidelberg, Melbourne,
Australia.

K. F. HARDY
J. T. HUESTON.

## HEPATITIS CAUSED BY THE NEWER AMINE-OXIDASE-INHIBITING DRUGS

SIR,—We recently recorded [1] hepatitis caused by pheniprazine, phenelzine, and nialamide, and we have since encountered what seems to be the first death caused by phenelzine.

A woman of 71 became depressed after the death of her husband and was given phenelzine ('Nardil') 15 mg. t.d.s. Three months later, after a total dosage of approximately 3500 mg., and after a few days' heartburn she became jaundiced. When admitted to hospital two weeks later she showed deep jaundice but no other physical abnormalities. The total serum-bilirubin was 24 mg. per 100 ml., alkaline-phosphate 31 units, zinc-sulphate turbidity 15 units, thymol turbidity 8 units, serum albumin 2·9 g. and globulin 2·7 g. per 100 ml. After admission, she became progressively more drowsy and died in hepatic coma three days later. Atrial flutter developed during the last day of life.

Necropsy revealed a small liver with a mottled red and yellow surface. Histological examination of the red areas showed complete loss of parenchymal cells, with collapsed sinusoids remaining, while the yellow areas consisted of surviving liver cells. Around the portal tracts cellular regeneration was occurring. The appearances indicated subacute liver necrosis. In the heart, coronary atheroma was present but the myocardium and valves appeared normal.

It seems probable that the liver lesion was induced by the phenelzine. The extensive liver-cell necrosis was of the type caused by other amine-oxidase-inhibiting drugs—i.e., iproniazid and pheniprazine. While it is well established that only a small proportion of patients taking these drugs become jaundiced, when they do, liver damage is liable to be extensive and to carry a high mortality, particularly in the middle-aged or elderly female. There is no evidence to suggest that the newer amine-oxidase inhibitors are safer than iproniazid, and indeed with their increasing use we are encountering jaundice more frequently.

In the choice of drugs for the treatment of depression, the small but undoubted risk of inducing fatal hepatic necrosis with the newer amine-oxidase inhibitors merits very serious consideration.

C. D. HOLDSWORTH
MICHAEL ATKINSON
J. A. DOSSETT
WILLIAM GOLDIE.

Department of Medicine,
The General Infirmary,
Leeds.

SIR,—Dr. Holdsworth and his colleagues (Sept. 16) reported a serious form of hepatitis complicating treatment with monoamine-oxidase inhibitors. In view of the widespread use of these drugs, we feel that a further case should be reported.

A married woman of 50 was referred to hospital for investigation of jaundice on Nov. 6, 1961. Her illness began on Sept. 20, with nausea and anorexia. A few days later, morning vomiting began and persisted until admission. Jaundice was first noticed eleven days before admission and was soon followed by generalised pruritus. At no time did she have pain, and there was no history of jaundice or liver disease. She had been examined by one of us (P. E. D.) on Sept. 11 because of headache. At that time there was no jaundice and no hepatosplenomegaly.

She had been taking phenelzine ('Nardil') (15 mg. t.d.s.) since June, 1961, for a mild depression and had continued to take this drug until admission on Nov. 6. When her present illness began, she had taken a total of 4 g. of this drug.

She was deeply jaundiced and there was slight palmar erythema but no spider nævi. Axillary hair was normal. The liver and spleen were both enlarged two fingerbreadths below the costal margin. Both organs felt rather firm but were not tender. Other systems were normal.

*Investigations:*

Nov. 7: Serum-bilirubin 11·3 mg. per 100 ml.
Gamma-globulin 9 units.
Alkaline-phosphatase 24 units.
Serum-protein 5·3 g. per 100 ml.
Albumin globulin ratio 1·7/1.
Serum glutamic-pyruvic transaminase (S.G.-P.T.) 310 units.
Electrophoretic pattern normal.
X-rays of gall-bladder area and of chest normal.
Hæmoglobin 11·2 g. per 100 ml.
White count 6600 per c.mm. (polymorphs 71%, lymphocytes 27%, monocytes 2%).
Erythrocyte-sedimentation rate (Westergren) 6 mm. in 1 hour.
Prothrombin content 55%.

A provisional diagnosis of hepatitis due to phenelzine was made and the drug was stopped. After ten days the jaundice was perceptibly less, and nausea, vomiting, anorexia, and pruritus had disappeared.

*Serial investigations:*

Nov. 13: S.G.-P.T. 240 units.
Nov. 20: S.G.-P.T. 220 units.
Nov. 24: S.G.-P.T. 140 units.
Serum-bilirubin 6 mg. per 100 ml.
Nov. 30: S.G.-P.T. 80 units.
Serum-bilirubin 4·3 mg. per 100 ml.
Serum-alkaline-phosphatase 17 units.
Serum-protein 5·1 g. per 100 ml.

This syndrome is similar to that described by Holdsworth et al. The illness, which resembled infective hepatitis at its onset, has run a protracted course. At the moment, three months after the onset of the illness and six weeks after the phenelzine was stopped, the patient is still faintly jaundiced and the liver and spleen are still palpable. It is too early to say whether complete resolution will occur or whether the patient will be left with permanent liver damage.

While we believe this to be a rare toxic effect of phenelzine, we have reported it because of its seriousness.

P. EDWARD DIPPLE
D. MEREDITH WILLIAMS.

Royal Gwent Hospital,
Newport, Mon.

## PRESSURISED OXYGEN FOR TOTAL BODY PERFUSION

SIR,—After we introduced pressurised oxygen as a new field for research in surgery in 1956,[1] the next publication on this principle came two years later from the Glasgow team.[2] Mr. Weale's paper (Sept. 9) from a third centre, however, is not directly concerned with the new principle in surgery. He used pressurised oxygen to accelerate oxygenation of hæmoglobin in a heart-lung machine and to reduce the quantity of the priming blood in the machine.

When the blood leaves the oxygenator and enters the patient, however, it has already returned to normal atmospheric pressure and consequently the quantity of oxygen in physical solution is no longer three times higher than when using oxygen of normal pressure. There is no difference for the patient whether this blood is oxygenated in a high-pressure oxygenator or in a usual one.

1. Holdsworth, C. D., Atkinson, M., Goldie, W. *Lancet*, Sept. 16, 1961, p. 621.

1. *Arch. Chir. neerl.* 1956, **8**, 193.
2. Smith, G., Lawson, D. A. *Scot. med. J.* 1958, **3**, 346.

The patient breathing oxygen in a high-pressure operating-room is drenched with physically dissolved oxygen. Hæmoglobin, plasma, and intracellular fluid, probably even all the cells of the body, contain an increased quantity of oxygen in physical solution. This made it possible to double the time of circulatory arrest with survival, so that an animal could live after complete extraction of the red cells and several patients with various diseases, such as gas gangrene, could be cured completely. These achievements are not, as Mr. Weale suggests, based on the same principle as is this ingenious heart-lung machine.

Wilhelmina Gasthuis, Amsterdam. I. BOEREMA.

*** We showed Professor Boerema's letter to Mr. Weale, whose reply follows.—ED. L.

SIR,—Whether benefit is derived from the total enclosure of an animal in a pressurised oxygen chamber or whether the rate of oxygenation is increased in a pressurised heart-lung machine, the principle is the same: it is the practical application of Henry's law.

Of course the oxygen pressure must be reduced prior to entry into the patient; hence the need for the heavy arterial clamp in my machine. It is inaccurate to state that blood has returned to normal atmospheric pressure, because it never falls below arterial pressure, and that is always above atmospheric. Incidentally, hæmoglobin must not be included in the substances capable of physical supersaturation.

Professor Boerema's work did not in fact inspire the design of this machine, but a search of the literature on the subject of pressurised oxygen revealed his previous and successful application of the same principle.

St. Bartholomew's Hospital, London, E.C.1. F. E. WEALE.

## THE G.N.C. AND THE S.R.N.

SIR,—The medical council of this hospital warmly welcomes the letter of Dec. 9 from the chairman of the St. Helier Group Medical Advisory Committee and his colleagues.

This hospital, a general one of 180 beds, with a large out-patient department, has had a nurse-training school since 1906. Over the years we have had a very high percentage of passes (93·4%) in the final examination for State-registered nurses and have had little difficulty in recruiting nurses.

The new regulations of the G.N.C. will remove our hospital and others of less than 300 beds from the approved list of training schools for State-registered nurses.

We are of the opinion that should these regulations be implemented without revision they will lead to a further reduction in nurse recruitment and to a lowering of the standard of nursing services available to the patients.

Miller General Hospital, Greenwich, London, S.E.10. G. E. THOMAS Chairman, Medical Council.

## COLLECTION OF MIDSTREAM SPECIMENS

SIR,—For many years now I have provided a 'Pyrex' glass gravy-boat for the collection of urine specimens in women. It is much easier to use than a chamber-pot, bowl, or kidney-dish, since its shape and the handle make it easier to pass between the thighs while sitting on a W.C., and for a midstream specimen the unwanted portion is easily voided into the pan.

Its sterilisation presents no problem either by boiling or dry heat, and if there is a fear that the pouring lip may have been contaminated by contact with the anus this can be flamed. The great majority of specimens collected for me by this method have been for chemical tests only for protein and sugar; but a reasonable number which have been sent for bacteriological examination have been reported sterile.

I feel quite sure it is an advance on either the "sterile wide-mouthed jar" or the "stainless-steel sputum mug" mentioned in Dr. Turner's interesting article of Nov. 11.

London, W.1. E. G. HUXLEY COWEN.

## RUPTURE OF THE POSTERIOR URETHRA

SIR,—I was interested in the case reported by Mr. Qvist,[1] who enunciates some very sound principles, which are unfortunately not always easy to apply in these cases. The object of treatment is not only to procure anatomical alignment, but also to prevent stricture formation.

Stricture formation is favoured by:

(1) Organisation of hæmatoma and extravasated blood: these should therefore be evacuated.

(2) Sepsis, which may be introduced by preoperative attempts at catheterisation. Instrumentation should be avoided, and if diagnosis is uncertain urethrography gives much more useful information and is less traumatising.

(3) It is well known that urine can cause necrosis not only of raw tissue but even of intact skin. It is therefore important to prevent urine reaching the damaged urethra, and urinary diversion is essential in all cases.

(4) Urethral instrumentation in the early postoperative period, which may only further damage freshly formed epithelium. Routine postoperative bouginage should, therefore, be avoided.

(5) Irritation by foreign body in the form of a catheter. Wilkinson [2] found no strictures in 6 cases treated by traction on a Foley's catheter, but this series is small. Johnston [3] feels that traction is essential to avoid stricture, fistulæ, and incontinence.

Certainly accurate realignment is important; but if this can be obtained without the use of a catheter one would expect the incidence of stricture formation to be even further reduced.

Ideally this could be achieved by direct suture, but this may be technically very difficult in cases of intrapelvic rupture of the urethra. Hugh Young, [4] with extensive experience of perineal exposures of the prostate, favoured the repair of an intrapelvic rupture through a perineal approach. Hunt and Morgan [5 6] also used a perineal approach; the triangular ligament is divided on each side and hinged forward, the prostate being pushed down by an abdominal operator.

Another technique which is worthy of note is to pass a suture through the anterolateral aspect of the prostate on either side; these two sutures are then passed through the perineum and tied on the skin over a gauze or rubber roll.[7 8] If good apposition can be obtained, it would be tempting to do without a urethral catheter; failing this a thin catheter round which exudate can escape might be used.

One further point may be of interest. The "railroading" of sounds may be difficult, and I have found the following technique simple in getting a catheter across a complete tear. A Foley catheter is passed up the urethra as far as it will go. It is a simple matter to lift its tip out of the retropubic space with a finger. A Jacques catheter is then passed through the open bladder and negotiated through the internal meatus and its tip similarly lifted out of the retropubic space. The two catheter tips are united with a suture, and traction on the Jacques

1. *Lancet*, 1961, i, 1406.
2. Wilkinson, F. O. W. *ibid*, p. 1125.
3. Johnston, J. H. *ibid*. p. 1406.
4. Young H. H. *J. Urol*. 1929, **21**, 4, 417.
5. Hunt, A. H., Morgan, C. N. *Lancet*, 1942, ii, 330.
6. Hunt, A. H., Morgan, C. N. *ibid*. 1949, i, 601.
7. Kisner, C. D. *S. Afr. med. J*. 1958, p. 1105.
8. Joubert, J. D. *ibid*. p. 919.

catheter will now draw the Foley catheter into the bladder without difficulty.

Port Elizabeth,
Cape Province. D. DE. G. VILLET.

### WEST KENT MEDICO-CHIRURGICAL SOCIETY

Dr. R. L. MEYRICK writes:

"May I ask your help in an inquiry I am making on behalf of the West Kent Medico-Chirurgical Society? This society, now 106 years old, is one of the older established London societies, and I am collecting material and information regarding the activities of the society since its inception. I should be very grateful if any of your readers having information about the society, including copies of the transactions or programmes or, indeed, copies of Purvis orations, would be good enough to allow me a sight of these documents. If the owner has no further use for them, the society would be most grateful to accept relevant papers, photographs, or other material. They may be sent to me at 80, Torridon Road, London, S.E.6."

## Obituary

### EARLE CHRISTMAS GRAFTON PAGE

P.C., G.C.M.G., C.H., M.B. Sydney, Hon. D.Sc., F.R.A.C.S., Hon. F.R.C.S.

Sir Earle Page brought to his career as a politician the experience of a medical training and years of practice, and as Minister of Health from 1949 to 1956 he was the architect of the Australian health scheme. He died on Dec. 20 at the age of 81.

*Associated Newspapers*

He was the son of a Grafton coach-builder, and he was educated at Sydney High School and at Sydney University. Soon after he graduated M.B. in 1902 he settled at South Grafton, where his practice extended over an area 80 miles wide by 200 miles long. His interest in public work began at this time; and he pioneered the Nymboida Electric Scheme, which was the first in Australia to charge a flat rate for farm and urban electricity. During the 1914–18 war he served with the Australian Forces as senior medical officer in H.M.A.S. *Ballarat*, and as surgeon to an Australian hospital at Abassia and at a casualty-clearing station in France.

In 1918, after his return to Australia, he became mayor of Grafton, and the following year he was elected to the Australian Parliament, and shortly afterwards became leader of the Country Party. In 1923 he served for the first time as acting Prime Minister, and during the next ten years or so he deputised in this office several times and in 1939 held it briefly in his own right. He also served at different times as Minister of Commerce and Minister of Health. During his second period at the latter Ministry (1949–56) he was entrusted with the immediate duty of securing "a working arrangement with regard to health services". After studying the services in other countries he devised the present Australian scheme which relies largely on voluntary insurance supplemented by Government subsidies. It was introduced by steps, and in 1956, soon after the main stages were completed, he retired from the cabinet.

He had, however, many other interests, and had large farm and cattle stations in Queensland and New South Wales. He was an authority on water conservation, irrigation, and hydro-electricity, and had written widely on these topics. When the New England University College was set up in 1938 he became chairman of its council, and in 1955, when it attained full university status, he became its first chancellor.

Sir Earle Page was appointed P.C. in 1929, G.C.M.G. in 1938, and C.H. in 1942. He was elected to the honorary fellowship of the Royal College of Surgeons of England in 1941. His first wife, formerly Miss Ethel Blunt, died in 1958. His second wife, formerly Miss Jean Thomas, survives him, with three sons and a daughter of the first marriage.

### EDMUND CECIL BEVERS

C.B.E., M.A., B.M. Oxon., F.R.C.S.

Mr. E. C. Bevers, whose death on Dec. 13 we announced last week, will long be remembered in Oxford for his skill as a surgeon, his talents as an administrator, and his warmth as a friend.

He was born in 1876 in Oxford, the son of the late Edmund Augustine Bevers and he was educated there at St. Edward's School and St. John's College. He qualified from Guy's Hospital in 1901 and after holding house-appointments in London and in Oxford he spent three years teaching anatomy in the University of Oxford before he began to practise surgery. In due course he joined the staff of the Radcliffe Infirmary and he was also Litchfield lecturer in surgery in the university. During the 1914–18 war he served with the R.A.M.C. as a surgical specialist.

The war brought him back from retirement, and when the National Health Service was started he continued to serve the Oxford Medical School as chairman of board of governors of the United Oxford Hospitals. He was appointed C.B.E. in 1951.

L. J. W. writes:

"For some of us one of the compensations of the war was that it brought Mr. Bevers from retirement back to Oxford where he became vice-chairman of the committee of management of the Radcliffe Infirmary, working in a triumvirate of which Sir William Goodenough and Sir Farquhar Buzzard were the other members. This was a time when, as a result of the establishment of the Nuffield clinical professorships and the commencement of the wartime clinical school, accommodation at the Radcliffe Infirmary was subjected to strains for which it had never been intended. Bevers took a flat near the Radcliffe Infirmary and was in the hospital every day, devoting the whole of his time to its problems. He had spent his working life in Oxford, where he had established a great reputation as a surgeon and had earned 'honour, love, obedience, troops of friends'. I count him among the dozen people who have most impressed and influenced me in my life. Automatically one thought of him as Mr. Bevers, the *Mr.* implying confidence and respect. He had wisdom, the quality which shows itself in the ability to make judgments which time subsequently proves to have been right. In addition, he was an unusually good judge of men and it was expedient to defer to his opinion on an appointments committee. He was a good talker, with an endearing chuckle as he told of his surgical experiences in hospital and in private practice. Looking back one realises what an extraordinary unifying influence he had on the diverse group of intelligent and temperamental people who had been crowded into the Radcliffe Infirmary and who were prone to generate a good deal of heat in their interactions, like molecules under pressure. It was difficult to be cross when Mr. Bevers was so sensible and good-natured. It was a great joy to everyone when, despite his age, he was made the first chairman of the Board of Governors of the United Oxford Hospitals in 1948. His portrait, painted about this time, now hangs in the entrance hall of the Radcliffe Infirmary and preserves the memory of one of the founding fathers of the Oxford Clinical School."

### RODNEY STEPHEN WALSH

M.A., B.M. Oxon., F.F.A. R.C.S., D.A.

Dr. Rodney Walsh, who had recently been appointed consultant anæsthetist to the Royal Dental Hospital, London, died on Nov. 18 as a result of an accident.

He was born in 1927, and he was educated at Sherborne and New College, Oxford, before coming to St. George's Hospital as a scholar in 1947. He won the Brackenbury prize in surgery in 1950, and after a surgical house-appointment spent a period in the Army doing National Service. He became resident anæsthetist at the Middlesex Hospital and later registrar and then senior registrar in anæsthetics in the Southampton group of hospitals and St. George's Hospital. He won the registrar's prize of the Section of Anæsthetics of the Royal Society of Medicine in 1961.

D. D. C. H. writes:

" Dr. Walsh showed outstanding ability and had already made a name for himself in the practice of anæsthesia. He was the author of a book on dental anæsthesia, and his winning paper for the registrar's prize was on the treatment of respiratory paralysis, in which he had shown great knowledge and skill. He was a keen observer and was continually engaged in new projects of research."

## Diary of the Week

DEC. 31 TO JAN. 6

**Wednesday, 3rd**

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1

8 P.M. *Surgery.* Mr. D. W. Parsons: Treatment of the Septic Hand. Mr. John Bradbeer: Complications of the Use of Non-absorbable Sutures in Gastrectomy. Mr. Harold Ellis: Experimental Study of the Ætiology of Post-operative Adhesions.

**Thursday, 4th**

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2

5 P.M. Mr. David Annis: Study of the Regenerative Capacity of the Epithelial Lining of the Urinary Bladder, together with Evidence Concerning the Function of the Mucosa in the Reflex Act of Micturition. (Arris and Gale lecture.)

ROYAL SOCIETY OF MEDICINE

8 P.M. *Neurology.* Dr. R. H. Dobbs, Dr. L. I. Woolf, Dr. G. A. Rose: Inborn Errors of Metabolism.

**Friday, 5th**

ROYAL SOCIETY OF MEDICINE

6 P.M. *Anæsthetics.* Dr. E. J. Ross, Mr. Bernard Harries, Dr. David Edwards, Dr. A. I. G. Robertson: Management of Cases of Phæochromocytoma.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1

3.30 P.M. Mr. William McKenzie: Treatment of Acute Inflammation in the Ear.

5.30 P.M. Mr. N. Asherson: Uncommon Diseases of Childhood.

## Appointments

BLACK, A. L., CH.M. Lpool, F.R.C.S.: general surgeon, Rotherham and Mexborough hospitals.

HARGREAVES, G. K., M.B. Edin., M.R.C.P.E.: consultant dermatologist, Stockport and Buxton, Macclesfield and district, and South Cheshire hospital groups, Manchester and Salford Hospital for Skin Diseases, and Victoria Infirmary, Northwich.

JONES, J. R., M.B., B.SC. Wales, D.P.H., D.OBST.: deputy county M.O.H. and M.O.H., joint district councils, Cardiganshire.

MCCALLUM, A. H., M.B. Cape Town, F.R.C.S.E., D.M.R.T., D.M.R.D.: consultant radiologist, Salford hospital group.

MCGINNESS, W. J., M.B. St. And.: deputy medical superintendent, East and West Fife hospital groups.

MACKAY, D. H., M.R.C.S., D.T.M. & H., D.P.H.: resident medical superintendent, Hammersmith Hospital, London.

**Dundee health and welfare department:**

BENSON, CHRISTINE, M.B. St. And.: assistant M.O., child health service.

LESSLIE, NONA S., M.B. St. And., D.P.H.: senior assistant M.O., child health service.

MCEWAN, SARAH C., M.B. Glasg., D.OBST., D.P.H.: assistant M.O., child health service.

**Colonial Appointments:**

ADAMS, W. E., M.B. N.U.I., D.P.H., D.C.H.: principal M.O., British Guiana.

DE BEAUX, J. L. M., M.B. Madras, F.R.C.S., D.T.M. & H.: surgeon specialist, Fiji.

DINGLEY, E. R., M.B. Lond., D.O.: M.O. (ophthalmology), North Borneo.

FULLER, ANGELA D., M.B. Cantab., D.C.H., M.O. Gambia.

HU, SHIH CHANG, M.B. Hong Kong, M.R.C.P.E., D.C.H.: specialist (pædiatrics), Hong Kong.

LETT, ZOLTAN, M.D. Czechoslovakia, F.F.A. R.C.S.: senior specialist, Hong Kong.

SAHAI, SANKAR, M.B. Lond.: M.O., British Guiana.

STONHAM, J. K., M.R.C.S.: M.O., Hong Kong.

TAKOOR, RAMAWAD, M.B. Belf.: M.O., special mobile force, Mauritius.

THOMPSON, MARGARET J., M.B. Dubl.: M.O., Jamaica.

WANG, RAYMOND SHENG-WU, F.R.C.S.E.: specialist (surgery), Hong Kong.

## Medicine and the Law

### Standard of Proof of Insanity in Divorce Cases

A HUSBAND petitioned for divorce on the ground of the wife's incurable unsoundness of mind. The Official Solicitor, as the wife's guardian *ad litem*, contested the suit on the basis that the wife was not incurably of unsound mind.

The medical superintendent of the mental hospital in which the wife had been a certified patient since 1936, suffering from schizophrenia, when asked his opinion of the wife's mental condition, said that it was most unlikely that she would make a full social recovery. The wife was 56 years of age. The judge stated that he was unable, on the evidence before him, to hold that the husband had proved his case. The case was adjourned, and at the resumed hearing a consultant psychiatrist, who had examined the wife in the interval between the two hearings, stated that in his opinion the wife was an improved, " burned out " schizophrenic, still showing residua of the illness, for which there was no medical cure, and unlikely to be substantially improved by further rehabilitation and retraining, and that she would remain of unsound mind. The chances of recovery were infinitesimal, and he considered it reasonable to express the view that the wife was incurably of unsound mind.

Mr. Commissioner LATEY, Q.C., said that the further evidence had satisfied him that the wife was, at the present time, incurably of unsound mind. It was important to observe that, in view of the changes which had taken place in recent years in the treatment of mental disorders, changes which were reflected in the changes in the law effected by the Mental Health Act, 1959, the relatively slight evidence of incurability which would have sufficed twenty years ago to establish the ground for relief could no longer be safely relied upon. The husband would be granted a decree nisi.

Greer *v.* Greer—*Probate, Divorce and Admiralty Division.* Mr. Commissioner Latey, Q.C. Nov. 20, 1961. Counsel and solicitors: Peter Archer (Geddes, Young & Co.); B. H. Pearce (Official Solicitor).

D. R. ELLISON
Barrister-at-Law.

## Parliament

### QUESTION TIME

#### The Lewisham Experiment

Lord TAYLOR asked the Government to provide details of the Lewisham experiment—Lord NEWTON replied: This is a survey, sponsored and financed by the King Edward VII Hospital Fund for London, which is being undertaken by the Government Social Survey. It covers a sample of households in Lewisham which include people aged 65 and over. The questions asked are designed to discover the ability of the old people to cope with the daily problems of living in their own homes, their mobility, and the use made of the health and welfare services available to help them. The survey will also show whether there are old people in need of help who are unknown to the statutory and voluntary bodies responsible for providing the services they need. The field work started in April this year and it is hoped that the final report will be available in 1962.

#### Young Disabled People

On Oct. 16 there were 3168 boys and 2607 girls on the Disabled Persons Register. Facilities for training disabled young people are available at 17 industrial rehabilitation units, 13 Government training centres, and 4 residential training colleges for the disabled.

# Notes and News

## MEDICAL STAFFING OF HOSPITALS

A Ministry of Health memorandum [1] sets out the action which hospital authorities should take in accordance with the recommendations of the Joint Working Party on the Medical Staffing Structure in the Hospital Service.[2]

*Review of medical staffing.*—Boards are asked to undertake a comprehensive review of medical staffing in their hospitals. After consultation with the Joint Consultants Committee the Minister has appointed a panel of consultants to act as assessors. Two of these assessors should be invited to join a board's review committee.

*Senior registrars.*—Boards are asked to establish for each regional hospital board area a joint advisory committee on senior registrars, consisting of medical members only. This committee should be requested as one of its first tasks to consider existing training arrangements and to advise on the development and organisation of rotational schemes between teaching and non-teaching hospitals. It will also advise whether registrars who fail to secure a consultant appointment after five years should continue in that grade or be transferred to the new intermediate grade.

*New intermediate grade.*—Decisions on boards' recommendations as to the number of posts in this grade will be made centrally on the advice of a professional advisory committee. A date for the introduction of the grade will be notified to the boards after their proposals have been approved. The precise type of grade, its extent, and its title will only be decided after the submission of the boards' proposals and after consultation with the Joint Consultants Committee. The salary scale will be a matter for settlement by Committee B of the Medical Whitley Council. The Minister has agreed that after the introduction of the new grade no more senior hospital medical officers or senior casualty officers should be appointed and no increases made in the sessions of part-time holders of these appointments.

## IDOLATRY OF NUMBERS

SPEAKING at Birmingham on Dec. 15, Mr. Enoch Powell, the Minister of Health, suggested that this was an age given to "the idolatry of numbers," when mere magnitude was apt to claim more respect than it deserved. In his view quality mattered more. He was discussing the suggestion of the McNair Committee in 1954 that we needed 4000 more dentists. Mr. Powell considered that the 37% increase in the number of treatments given during 1960 suggested an alternative method of making good the defect, and one which might be applied to other professions.

The McNair report, he said, was one of many weighty and well-founded appraisals which had informed us that we needed so many thousand more of this profession, so many thousand more of that profession, all round the compass. It was not his intention to cast doubt on any of these assessments, but it was unlikely that the sum total volume of aptitudes in the population was increasing at anything near the rate which would be needed to fulfil them. The secret of human advancement had been how to make a given amount of manpower or brainpower yield always more output and bigger results. Applying this to the National Health Service in general, he predicted that in 10 or 20 years' time its progress would be found to have depended less on an absolute increase in the professional staff of all kinds, medical and other, who worked in it—though such an increase there would no doubt have been—than upon an increase in the quantity of medical care and treatment which a given quantity of staff would be able to furnish.

## MANUAL OF NUTRITION

IN the latest edition of this sensible little manual [3] and well-established favourite, it has been possible to revise all the tables which give the content of the various nutrients in foods. These are now based on the new edition of *The Composition of Foods* by McCance and Widdowson.[4] It sets out in simple language the elementary physiology of nutrition and the nutritive value of the common British foods. Doctors can recommend it to those patients, such as diabetics and the obese, who should know the elements of these subjects; and it will also help nurses and anyone concerned with public health and health education. The information is accurate, up to date, and well chosen to meet the needs of those with no previous knowledge of the subject.

1. H.M. (61) 119.
2. Medical Staffing Structure in the Hospital Service: report of the joint working party. H.M. Stationery Office, 1961. See *Lancet*, 1961, i, 649, 657.
3. Manual of Nutrition. Ministry of Agriculture, Fisheries and Food. Sixth edition. Obtainable from H.M. Stationery Office. Pp. 79. 3s.

## APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued amendments to chemical names in the latest supplementary list of approved names [5] as follows:

| *Approved name* | *Chemical name* |
|---|---|
| Sodium Metrizoate | Sodium 3-acetamido-2:4:6-tri-iodo-5-*N*-methyl-acetamidobenzoate |
| Thiethylperazine | 2-Ethylthio-10-[3-(4-methylpiperazin-1-yl)propyl] phenothiazine |

4. McCance, R. A., Widdowson, E. M. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1960, no. 297.
5. See *Lancet*, Dec. 23, 1961, p. 1417.

## University of London

The title of reader in chemical pathology has been conferred on Dr. P. G. Walker in respect of his post at the Institute of Orthopædics.

## University of Birmingham

On Dec. 15 the following degrees were conferred:

*Ch.M.*—Geoffrey Slaney, J. A. Williams.
*M.B., Ch.B.*—R. W. Adams, P. C. Allen, A. J. Banks, Ekpo Edet Ekpo Bassey, Ina K. Burdick, B. J. Cooper, Joseph Cox, N. K. Gostick, P. S. Ireland, Lesley P. Levy, J. K. Portwood, Jenifer A. Shaw, W. R. Shortland-Webb, D. F. Smallbone, M. J. Tonks.

## University of Bristol

At recent examinations the following were successful:

*M.B., Ch.B.*—Audrey K. Ball, H. V. Poku, P. J. Thomas.
*D.P.H.*—Lotfollah Ziaee.

## University of Durham

On Dec. 16 the following degrees and diploma were conferred:

*Ph.D. in medicine.*—Abdul Rahman Ghani (in absentia).
*M.S.*—D. S. Chapman.
*M.B.B.S.*—J. W. Barton, Emanuel Pooranmal Bedessee, Wilkinson Glendinning, Elizabeth H. Gregory, James Hardy, Maureen O'Byrne, Julius Akanji Okuboye, J. D. Robinson, Maria E. S. Szatrowska, D. G. Windsor.
*D.P.M.*—D. H. MacKenzie.

## University of Leeds

At recent examinations the following were successful:

*M.D.*—J. T. Rose.
*M.B., Ch.B.*—D. R. Richmond (first-class honours), F. E. Hargreave, Rosemary J. E. Saword, J. B. Stoker (second-class honours), Thelma S. Adams, D. P. Addy, J. L. Barton, M. McD. Bell, J. S. Buisson, G. A. Bunch, B. S. Coleman, Doreen A. Ducat, A. M. Dufton, J. B. Dyson, A. B. Gudgeon, B. C. Hutchinson, J. I. Joannides, B. W. Joseph, T. A. Kerr, Cristina O. Leake, Lila M. Malhotra, R. L. Marks, E. F. H. Moll, M. D. Moore, D. B. Oughtibridge, Roy Pollard, G. C. Savva, J. R. Sherwin, D. C. M. Smith, J. A. Spencer, Margaret E. Spencer, Julia Swallow, Faye Walden.

## University of Liverpool

On Dec. 15 the following degrees were conferred:

*M.D.*—N. T. Burnett, W. K. Cowan, E. R. Evans, L. J. Hipkin, W. J. Stanley, R. Whitehead.
*Ph.D. (in the faculty of medicine).*—D. R. Bowsher.
*M.Ch. Orth.*—B. K. Datta, H. Dovey, G. S. W. Fung, M. M. Hifny, K. G. Kling, W. J. Laister, J. N. A. Livingstone, V. K. Pillay, L. P. Seimon, T. N. Shanmugalingam, J. G. Sweeney, D. G. Wray, K. H. Yeoh.
*M.B., Ch.B.*—N. M. Blok, J. Burns, D. P. H. Caldwell, D. Carrigan, H. I. Davies, T. France, E. N. Marks, L. R. Priaulx, W. J. Thompson.

A Warrington Yorke medal in tropical hygiene has been awarded to Anne Sherratt and G. J. Thorpe. At recent examinations the following were successful:

*D.T.M. & H.*—D. S. U. Ahmed, D. E. Brooke, Mollie Dada, T. O. Dada, R. G. Datar, N. A. De Heer, S. Fogh, B. B. Guha Thakurta, R. B. Hunton, A. F. M. S. Islam, Brigid P. Kelly, Sudchit Lauhachinda, M. A. McFadyen, P. F. Mead, R. W. Moyes, B. P. V. O'Duffy, D. A. Ogbe, O. Olasimbo, V. B. Olsen, Carolyn E. Ritchie, J. H. Sewart, Anne Sharratt, D. P. Shepherd, K. C. Simpkins, A. O. Sobo, D. J. D. Stevenson, Khan Taj-Ud-Din, G. J. Thorpe, Hazel M. Wilson, S. B. Wimalasuria.
*D.M.R.D.*—Margaret D. Burke, R. Spencer.
*D.M.R.T.*—M. K. Mitter, Norma S. Strelitz.

### University of Sheffield

Dr. F. A. Best has been appointed research assistant in obstetrics and gynæcology, and Dr. George Meachim lecturer in pathology.

### University of Aberdeen

On Dec. 13 the following degrees were conferred:

*Ch.M.*—J. G. Murray.
*M.B., Ch.B.*—F. G. Adams, I. J. C. Dunbar, B. D. M. Grassick, J. M. Hunter, Iqbal Hussain Khan, Evelyn Stewart.

### University of Edinburgh

On Dec. 15 the following degrees and diplomas were conferred:

*M.D.*—*T. P. S. Powell (commended); R. J. Henderson.
*M.B., Ch.B.*—I. M. Cachalia, A. T. Campbell, B. P. Clarke, I. T. Davie, G. D. K. Flint, G. P. Gilby, P. N. Grannum, A. F. Harper, J. S. Hirschowitz, B. J. Ivey, D. P. Kay, Oluyemisi Adeniyi Kuforiji, David Morris, T. G. Plunkett, D. G. S. Reid, J. W. Turvey, E. P. Woodings.
*D.P.H.*—Nevres Baykan.
*D.M.R.D.*—N. W. T. Grieve, J. G. B. Russell, William Urquhart, G. B. Young.
*D.P.*—Felix Kojo Amarquaye, Israel Kolvin, R. E. Mackie.
* In absentia.

### Royal College of Surgeons of England

At a meeting of the council on Dec. 14, with Sir Arthur Porritt, the president, in the chair, Surgeon Lieut.-Commander John Hunter Sewart was presented with the Gilbert Blane medal. Sir Stanford Cade was appointed Hunterian orator for 1963. The following lecturers were appointed for 1962: Sir Eric Riches (Bradshaw); Mr. H. Osmond-Clarke (Robert Jones); Dr. W. S. C. Copeman (Thomas Vicary); Prof. H. J. Seddon (Watson-Jones). The Hallett prize was presented to Dr. P. V. Mills.

Diplomas of fellowship were granted to the following:

J. S. Winter, J. G. Gill, J. E. Bridger, D. F. Woodhouse, G. M. B. Bulman, Dorothy J. Whitney, John Atkins, M. C. Rang, P. J. Stiles, J. L. Provan, G. B. Williams, Mohamed Kamal El-Din Hussein El-Rifi, Soli Jamshed Lam, H. R. M. Roberts, M. E. J. Hackett, Musa Sadiq Nakash, Ismail Amin Nabri, Doreen A. Birch, Amarendra Chaudhury, Bhogilal Prabhudas Gandhi, Alwyn Wilkinson, Adel Bassily Guirguis, J. A. M. Martin, Chintamani Vinayak Mehendale, Robert Pringle, Kamal Tewfik Said, J. H. Youngleson, Lynne W. Baker, L. R. Celestin, Avinash Chander Chadha, J. McP. Drummond, Ranjit Kumar Guhathakurta, C. B. Grieve-Dingwall, J. N. Taylor, P. K. Coakley, Roy Dalgleish, H. W. McFarlane, B. A. Messmer, G. J. Rice, Surendra Bhogilal Shah, Cedric Susanga Wickramasuriya, J. H. Bulmer, J. A. S. Dickson, Kallakurchi Gopinatha Rao, J. S. Hopkins, J. O. N. Lawson, J. W. Richardson, J. A. Southam, Abdel Khalik Moustafa Terzaki, S. G. Thompson, L. H. Wright, Alan Bracewell, H. E. Clifford, Sherali Hassanali Dhalla, Louis Gecelter, Glyn Jones, Imdad Hussain Khan, Thomas Lo, M. J. Loughlin, J. H. McKessar, Bimalendu Mukherjee, W. McN. Orr, Vithal Gangadhar Phansalkar, P. H. Smith, T. McI. Stevenson, J. P. A. Weaver, Bernard Welford, A. T. Williams, W. H. Cadzow, S. D. Clarke, J. D. Ellis, K. P. Ferris, Amin Habashi Flota, F. J. Ham, Manmohan Kapur, A. G. MacIntyre, Ruth V. Magnus, P. N. Mangos, Dilip Kumar Mukherjea, S. W. Parkinson, Salil Roy Chowdhury, W. N. Tucker, J. A. K. Wightman, Margaret J. Witt, Henry Byrne, K. M. Fuller, Subramaniam Kalyanaraman, J. G. Lester, Karimpat Mathangi, Ajay Kanti Poddar, Somendra Mohan Sengupta, Nasirahmed Bashirahmed Shaikh, Hyder Ismail Sheikh, R. L. Smith, R. D. Stedeford, A. W. Swanton, David Sykes, D. W. Wilson, H. B. Devlin, Somnath Jaivant Gude, D. I. Hamilton, Geoffrey Hoyle, D. C. Humphrey, Ariyasinghe Edmund Kulatilake, M. J. Notaras, J. P. O'Collins, Manhar Vidyanand Patel, Inder Perkash, Arumugam Selvaratnam, Madan Mohan Sharma, M. J. Solan, R. M. Tracey, Sumitra Felix Wickramasinghe, W. G. Pearce, B. D. Shepherd.

Diplomas of membership were granted to T. C. M. Andrews and P. M. Worrall.

Dr. O. H. Wangensteen will give a Moynihan lecture on Wednesday, Jan. 10. His subject will be the stomach since the Hunters—gastric temperature and peptic ulcer. Mr. F. W. Holdsworth will give a Watson-Jones lecture on Thursday, Jan. 11. He will speak on fractures, dislocations, and fracture-dislocations of the spine. Both lectures will be at 5 P.M. at the college, Lincoln's Inn Fields, London, W.C.2.

### Society of Apothecaries of London

At recent examinations the following were successful:

*M.M.S.A.*—T. E. Dada, K. M. Huntington.
*L.M.S.S.A.*—D. K. Chaudhari, N. V. Edwards, P. P. Fanning, S. Ganesh, M. A. Halim, B. W. Loh, P. W. A. Manzell, M. A. Penn, S. S. Raghavan, R. H. F. Waitt.

### Royal Faculty of Physicians and Surgeons of Glasgow

Prof. C. E. Dent will give a Walker lecture on Tuesday, Jan. 9, at 5.15 P.M., at the faculty, 242, St. Vincent Street, Glasgow. He will speak on inborn errors of aminoacid metabolism.

### Royal College of Surgeons in Ireland

*Faculty of Radiology*.—This faculty has been inaugurated by the college. Before holding examinations for the fellowship of the faculty, the council will award a limited number of fellowships to consultants who have been practising radiology for not less than ten years. Radiologists who wish to be considered should send particulars to the registrar of the college, St. Stephen's Green, Dublin.

### Institute of Diseases of the Chest

Clinical demonstrations will be arranged by Dr. F. H. Scadding at the Institute, Fulham Road, London, S.W.3, on Fridays, at 5 P.M., from Jan. 5 to March 23.

### Birmingham Regional Hospital Board

Sir Arthur Thomson, F.R.C.P., has been appointed chairman of the board in succession to Sir Edward Thompson who has resigned.

### Academy of Medicine, Singapore

The office-bearers for the year 1961–62 are as follows:

Master, Dr. Gwee Ah Leng; assistant master, Prof. Yeoh Ghim Seng; scribe, Mr. Choo Jim Eng; bursar, Dr. Khoo Oon Teik; bedel, Prof. J. A. Jansen; censors, Prof. G. A. Ransome, Mr. D. W. C. Gawne, Dr. Ho Yuen, Mr. Y. Cohen, Dr. Wong Hock Boon.

### Royal Medico-Psychological Association

This Association is to hold a two-day lecture course on Monday and Tuesday, Feb. 12 and 13, at 1, Wimpole Street, London, W.1. The speakers will be Dr. B. H. Kirman, Dr. W. V. Wadsworth, Dr. S. H. Foulkes, Dr. John Bowlby, Dr. J. R. Smythies, Dr. Peter Dally, Prof. Ewen Cameron, and Prof. H. J. Eysenck. Tickets may be had from the secretary of the Association, 11, Chandos Street, London, W.1.

### Wellcome-Swedish Exchange Research Fellowships

The Wellcome trustees have entered into an arrangement with the Medical Research Council of Sweden for the establishment of a system of exchange fellowships, under which one British research-worker (or research trainee) in any branch of the natural sciences bearing upon human or animal medicine will be sent annually to work for one year at a research centre (or centres) in Sweden, and one Swedish research-worker (or research trainee) within the same range of disciplines will be supported at a centre (or centres) within the United Kingdom for a similar period.

The cost of the scheme, which is modelled upon the system of Carlsberg-Wellcome travelling research fellowships established jointly by the Carlsberg Foundation of Copenhagen and the Wellcome trustees in 1957, for the annual exchange of Danish and British research-workers and trainees, will be shared between the Swedish Medical Research Council and the Wellcome Trust. The fellowships will include stipends ranging from £1000 to £2000 per annum (or their equivalents in Swedish Kroner) according to seniority, together with provision for travelling and certain incidental expenses. It is intended that the arrangement shall become effective at the beginning of the academic year 1962-63, and invitations to apply for these awards will be published simultaneously with the next advertisement for Carlsberg-Wellcome travelling research fellows in March, 1962.

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Dr. P. C. Elmes has been appointed by the Royal Academy of Medicine in Ireland and the Medical Research Council of Ireland to give the Graves lecture for 1962.

A special general meeting of the members of the Auxiliary Royal Army Medical Corps Funds will be held on Monday, Jan. 8, at 4.45 P.M., at 11, Chandos Street, London, W.1.

From Jan. 1 the British Hospital for Functional Nervous Disorders is to be known as the Camden Clinic.

The 1960 edition of the Ministry of Power's *Digest of Pneumoconiosis Statistics* is in a new form which was recommended by a working party set up by the National Joint Pneumoconiosis Committee. It is no longer restricted to the mining and quarrying industries but also gives details of pneumoconiosis in some other industries. Some tables cover a run of years (1955-60) instead of only one year. Tables relating to deaths from pneumoconiosis and disablement benefits have been revised. Copies (3*s*.) may be had from H.M. Stationery Office.

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